Prenatal maternal stress and child ADHD symptoms in early childhood

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Tiivistelmä – Abstrakt – Abstract

Objectives. Exposure to maternal stress during pregnancy has been associated with a variety of adverse outcomes in the offspring, ranging from restrictions on fetal growth to long-term psychological impairments. Growing evidence suggests that prenatal maternal stress may also play a role in the onset of attention deficit hyperactivity disorder (ADHD). However, results from previous studies have not been uniform and methodological shortcomings may have impacted the findings. The aim of this study is to examine whether exposure to prenatal maternal stress is associated with higher levels of ADHD symptoms in the children, and whether the associations are timing-specific and independent of postnatal maternal and paternal stress.

Methods. The current study sample consisted of 2,304 mother-child dyads participating in the PREDO project who were recruited from maternity clinics at 12 + 0 to 13 + 6 weeks of gestation. The women filled out a reliable and valid stress self-report questionnaire, the Perceived Stress Scale (PSS), every two weeks throughout pregnancy, a total of 14 times. Child ADHD symptoms were reported by the mothers at child age of 1–5 years with the Conners' 10-item scale, concurrently with a repeated assessment of maternal stress. Paternal stress was evaluated with the PSS at child age of six months. The associations between prenatal stress and child ADHD symptoms were analyzed statistically using multiple linear regression, controlling for multiple sociodemographic and perinatal confounders and for postnatal levels of maternal and paternal stress.

Results and conclusions. Prenatal maternal stress was associated with significantly higher levels of ADHD symptoms in the offspring. Mid- to late-pregnancy stress had the strongest associations with child ADHD symptoms, while early-pregnancy stress showed a slightly weaker, yet significant, effect. The associations between prenatal stress and child ADHD symptoms were partially mediated by postnatal maternal stress. Nevertheless, even after controlling for postnatal maternal stress, the independent effects of prenatal stress remained significant. Adjusting for postnatal paternal stress had no impact on the effect sizes. The sex of the child moderated the association between first trimester prenatal stress and child ADHD symptoms, so that prenatal stress during the first trimester independently predicted higher levels of ADHD symptoms among boys, whereas, among girls, no significant associations were found for early-pregnancy stress after postnatal maternal stress was accounted for. Overall, the current findings are in line with the fetal programming hypothesis and highlight the importance of prenatal environmental factors in the etiology of childhood ADHD.

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Pregnancy, stress, timing, ADHD

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Äidin raskaudenaikaisen stressin yhteys lapsen ADHD-oireisiin varhaislapsuudessa

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Tiivistelmä – Abstrakt – Abstract

Tavoitteet. Äidin raskaudenaikaisen stressin on todettu olevan yhteydessä useisiin lapsen kehityksellisiin ongelmiin: niin sikiöaikaisiin kasvuhidastumiin kuin kauaskantoisiin psyykkisen kehityksen pulmiin. Viimeaikaiset tutkimukset ovat osoittaneet, että raskaudenaikainen stressi saattaa kasvattaa myös aktiivisuuden ja tarkkaavuuden häiriön (ADHD) riskiä. Tutkimustulokset ovat kuitenkin olleet osin ristiriitaisia ja menetelmälliset puutteet ovat saattaneet vaikuttaa tuloksiin. Tässä tutkimuksessa tutkitaan äidin raskaudenaikaisen stressin ja sen ajoittumisen yhteyttä lapsen ADHD-oireisiin. Lisäksi tarkastellaan, onko äidin tai isän stressillä lapsen varhaislapsuudessa vaikutusta edellä mainittuihin yhteyksiin.

Menetelmät.. Tähän tutkimukseen osallistui 2,304 PREDO-tutkimuksen äiti-lapsi paria. Äidit rekrytoitiin tutkimukseen äitiyspoliklinikoilta raskausviikoilla 12 + 0 – 13 + 6. Naiset täyttivät tilastollisesti luotettavan ja pätevän stressin itsearviointikyselyn (Perceived Stress Scale; PSS) kahden viikon välein koko raskauden ajan, yhteensä 14 kertaa. Lasten ollessa 1–5 vuoden iässä äidit arvioivat lasten ADHD-oireita (Conners' 10-item scale) sekä täyttivät uudestaan omaa stressiä mittaavan kyselyn. Isän stressiä arvioitiin PSS-mittarilla lapsen ollessa kuuden kuukauden ikäinen. Raskaudenaikaisen stressin yhteyttä lapsen ADHD-oireisiin tutkittiin tilastollisesti regressioanalyysillä huomioiden useiden sosiodemografisten tekijöiden sekä äidin ja isän postnataalisen stressin vaikutukset.

Tulokset ja johtopäätökset. Altistuminen raskaudenaikaiselle stressille oli tilastollisesti merkitsevästi yhteydessä lapsen voimakkaampiin ADHD-oireisiin. Raskauden keski- ja loppuvaiheeseen ajoittuneella stressillä oli vahvempi yhteys lapsen ADHD-oireisiin kuin alkuraskauden stressillä, jolla oli pienempi, joskin myös tilastollisesti merkitsevä vaikutus. Äidin postnataalisella stressillä havaittiin huomattava, edellisiä yhteyksiä medioiva vaikutus. Postnataalisen stressin huomioimisesta huolimatta yhteydet raskaudenaikaisen stressin ja lapsen ADHD-oireiden välillä säilyivät riippumattomina ja tilastollisesti merkitsevinä. Isän postnataalisen stressin kontrolloiminen ei vaikuttanut efektikokoihin. Lapsen sukupuolella havaittiin yhdysvaikutus 1. raskauskolmannekseen ajoittuneen stressin kanssa. Pojilla altistuminen stressille alkuraskaudessa ennusti voimakkaampia ADHD-oireita, kun taas tytöillä alkuraskauden aikaisen stressin yhteys ADHD-oireisiin ei säilynyt merkitsevänä, kun äidin ajankohtaisen stressin vaikutus huomioitiin. Tutkimuksen tulokset tukevat hypoteesia sikiöaikaisesta ohjelmoitumisesta ja korostavat raskaudenaikaisten ympäristötekijöiden merkitystä lapsen myöhemmälle ADHD-oireilulle.

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1 Introduction

Maternal exposure to stressful conditions during pregnancy has long-lasting effects on the child (Beydoun & Saftlas, 2008; Talge, Neal, Glover, & the Early Stress, Translational Research and Prevention Science Network, 2007; Weinstock, 2008). The association between prenatal physical conditions and child development is well established – poor nutritional level, lack of sleep and exercise as well as exposure to teratogens are known to have detrimental effects on the developing child leading to a variety of less than optimal outcomes (Bale et al., 2010; Chang, Pien, Duntley, & Macones, 2010; Hellerstedt, McGovern, Fontaine, Oberg, & Cordes, 2008; Marques, O'Connor, Roth, Susser, & Bjørke-Monsen, 2013). Research in the past years has provided strong evidence that the psychological well-being of the mother also impacts the development of the child.

Prenatal maternal stress refers to the objective strain or subjective distress experienced by the mother during pregnancy. Maternal stress during pregnancy has been associated with several adverse effects in the offspring, ranging from restrictions on fetal growth to long-term psychological impairments, including lower birthweights and preterm births (Wadhwa, 2005; P. Zhu, Tao, Hao, Sun, & Jiang, 2010), poorer cognitive outcome (Laplante et al., 2004) and increased risk of emotional and behavioral problems (O'Connor, Heron, Golding, Beveridge, & Glover, 2002; Rice et al., 2010; Van den Bergh & Marcoen, 2004). The specific mechanisms underlying the transmission of effects to the fetus have yet to be uncovered, but "fetal programming" – the permanent alteration in development caused by environmental stimuli *in utero* – is thought to play a central role (D. J. Barker, 1998).

Attention deficit hyperactivity disorder (ADHD) is the most common neuropsychiatric disorder among children (Wolraich et al., 2011) and is, therefore, a major public health concern. It is characterized by symptoms of inattention, hyperactivity and impulsivity, and the clinical expression varies greatly both between and within individuals (Brocki & Bohlin, 2006; Neuman et al., 2005). The etiology of ADHD is extremely complex and largely linked to genetic factors (Lichtenstein, Carlström, Råstam, Gillberg, & Anckarsäter, 2010). However, growing evidence suggests that environmental factors, especially during the fetal period, play a significant role in the onset of ADHD (Barkley, 2005). Maternal stress exposure during pregnancy has been proposed as one of these risk factors, and much of the research conducted has supported the association between prenatal stress and offspring

ADHD (Grizenko et al., 2012; Rodriguez & Bohlin, 2005; Ronald, Pennell, & Whitehouse, 2011). Nevertheless, the results from previous studies have not been uniform and methodological shortcomings may often have impacted the findings.

The aim of this study is to examine the association between prenatal maternal stress and attention deficit hyperactivity symptoms in the children. The present study is part of the longitudinal PREDO project and involves a total of 2,304 mothers recruited from nine Finnish hospitals in 2005-2010 (Villa et al., 2013). In contrast to much of previous research, this study contains prospectively collected data from a large community sample. Moreover, this study is unique in that it allows for controlling of postnatal paternal stress in the child's infancy and postnatal maternal stress concurrently with child ADHD symptom evaluation, neither of which have previously been examined in relation to prenatal maternal stress and child ADHD risk.

1.1 Prenatal maternal stress

Psychological stress refers to when environmental demands tax or exceed an individual's adaptive capacity (Cohen, Janicki-Deverts, & Miller, 2007). The definition of stress is broad and overlaps with psychiatric symptoms, such as anxiety and depression (Dunkel-Schetter & Glynn, 2011). Due to the difficulties in defining stress, research in the field has been conducted using various stress-related concepts, and the scope of study has often included psychiatric symptoms such as anxiety and depression. In the present study the focus is on maternal stress, and studies concerning psychiatric symptoms are referred to mainly in the absence of research focusing on more specifically defined stress.

Maternal stress exposure during pregnancy may vary in type, magnitude and length. Prenatal maternal stress caused by acute stressors, such as natural disasters or wars, has been associated with increased risks concerning both fetal development (Torche, 2011) and subsequent psychological development (Laplante, Brunet, Schmitz, Ciampi, & King, 2008). Chronic stress, such as daily hassles, work stress, marital issues and financial problems, have been associated with similar outcomes (Rini, Dunkel-Schetter, Wadhwa, & Sandman, 1999; P. Zhu et al., 2010), but the effects of chronic stress appear to be more robust and persistent overall (Richardson, Zorrilla, Mandyam, & Rivier, 2006). However, the emergence of acute

stressors may also lead to prolonged chronic stress (Yehuda, McFarlane, & Shalev, 1998), which makes it difficult to differentiate between the two.

The effects of prenatal maternal stress may also vary according to the severity of the exposure. A dose-response effect has been reported in several studies, where higher levels of maternal stress have resulted in more prominent adversities in the offspring (King et al., 2009; Laplante et al., 2004). However, this finding has not been replicated in all studies, as some have shown no differential effect of severity (Dancause et al., 2011). Furthermore, the duration of the stress exposure appears to be of particular importance, as higher rates of adverse effects have been noted as result of pregnancies with longer-lasting stress (Xu et al., 2013).

Although the prevalence of serious psychological distress appears to be lower during pregnancy than non-pregnancy (Ahluwalia, Mack, & Mokdad, 2004; Glasheen, Colpe, Hoffman, & Warren, 2015), experiencing a level of psychosocial stress during pregnancy is common (Woods, Melville, Guo, Fan, & Gavin, 2010). Prevalence estimates for prenatal maternal stress vary enormously in different studies (26–84 %; Rondo et al., 2003; Woods et al., 2010), largely depending on how "stress" is defined. Methodological issues, as well as the lack of a clear-cut definition of stress, pose challenges to determining a reliable estimate of occurrence.

The incidence of prenatal maternal stress varies in different populations. Researchers have found associations between increased stress and several factors, such as low socioeconomic status, young age, lack of social support, substance abuse and domestic violence (Boyd, 2002; Evans & English, 2002; Woods et al., 2010). The susceptibility to experience stress during pregnancy is multifaceted, and the impact of the aforementioned factors also varies by the type of stress (e.g. acute trauma vs. common life stress) experienced. In addition to problems with defining stress, experiencing stress during pregnancy raises the risk of having more depressive or anxiety symptoms (Maccari et al., 2003), which in turn increases the risk of adverse effects on the offspring (Field, Diego, & Hernandez-Reif, 2006; O'Connor et al., 2002).

The prevalence as well as the influence of prenatal stress may also vary according to the timing of the stress exposure. Mothers' sensitivity to stress diminishes towards the end of pregnancy, which leads to the subjective experiences of stress being highest earlier in

pregnancy (Kammerer, Adams, von Castelberg, & Glover, 2002; K. A. Matthews & Rodin, 1992). Fetal development, concurrently, strongly points to being characterized by sensitive periods (Talge et al., 2007). This is particularly well known with somatic development, where disruptions in fetal development cause malformations and abnormalities in the specific parts that are forming at that time (e.g. cleft lip during weeks 4–7 of pregnancy; Mossey, Little, Munger, Dixon, & Shaw, 2009). The same mechanism seems to apply to psychological factors, as the effects of prenatal maternal stress vary according to the developmental phase in which the fetus is during the stress exposure (Talge et al., 2007).

An important consideration regarding types of stress is the distinction between objectively and subjectively measured stress. The subjective experience of a stressful event may vary significantly depending on the personal characteristics of the expectant mother. When evaluating life events based on factual matters, Hedegaard, Henriksen, Secher, Hatch and Sabroe (1996) found no association with length of gestation or prematurity. However, when assessing the subjective experience, they found that women who experienced the events as highly stressful were more likely to have preterm deliveries. A similar result was found by Lipkind, Curry, Huynh, Thorpe and Matte (2010), who noted that only the women who showed signs of post-traumatic stress disorder had an increased risk of low birth weight and preterm delivery; experiencing the September 11 attacks in the proximity of the World Trade Center per se did not raise the risk. Nevertheless, if the objective measure of stress is severe enough, even the offspring of women who have not perceived the experiences as stressful have been shown to be affected (King, Dancause, Turcotte-Tremblay, Veru, & Laplante, 2012).

1.1.1 Prenatal stress and fetal development

The effects of prenatal maternal stress have become an increasingly important focus of study over the past years, as the exposure to stress during pregnancy has been shown to affect the developing fetus in a variety of ways. Regarding fetal development, the main focus of study has been on birth outcomes, and the most robust findings have been higher rates of preterm births and lower birthweights (Dunkel-Schetter, 1998; Wadhwa, 2005; P. Zhu et al., 2010). Maternal exposure to both chronic stress during pregnancy (Rini et al., 1999; Tegethoff, Greene, Olsen, Meyer, & Meinlschmidt, 2010b; P. Zhu et al., 2010) and acute stressors in

the 1st trimester (Precht, Andersen, & Olsen, 2007; Torche & Kleinhaus, 2012; P. Zhu et al., 2010) has been shown to increase the risk of prematurity and small-for-gestational age (SGA) births. Women affected by the September 11, 2001 terrorist attacks were found to have more infants with significant reductions in fetal growth: lower birthweights, shorter lengths at birth and smaller head circumferences as well as more SGA births (Ohlsson & Shah, 2011). In Sweden, following both the murder of Prime Minister Olof Palme in 1986 and the Estonia catastrophe in 1994 the rates of very low birthweight rose significantly (Catalano & Hartig, 2001). Exposure to earthquakes, especially in the first trimester of pregnancy, has also been found to increase the rates of preterm deliveries and SGA births (Glynn, Wadhwa, Dunkel-Schetter, Chicz-Demet, & Sandman, 2001; Oyarzo et al., 2012; Torche, 2011).

The findings of associations between prenatal maternal stress and adverse birth outcomes have been replicated at different points in pregnancy. Between the 16th and 30th week of pregnancy, subjectively assessed highly stressful life events have been associated with shorter gestational duration and higher risk of prematurity (Hedegaard et al., 1996). Pregnancy-specific anxiety at 28–30 weeks of pregnancy has also been reported to decrease gestation length rather than at 18–20 weeks (Mancuso, Schetter, Rini, Roesch, & Hobel, 2004), and higher rates of preterm delivery have been observed in relation to maternal distress at 30–36 weeks of pregnancy (Rondo et al., 2003). Although contradicting results have also come up (Pryor et al., 2003), exposure to prenatal stress at any point in pregnancy appears to pose a potential risk for decreased birthweight and shortened gestational duration, regardless of the type of stress experienced (Beydoun & Saftlas, 2008; Glynn et al., 2001; Mancuso et al., 2004; Rondo et al., 2003; P. Zhu et al., 2010).

1.1.2 Prenatal stress and psychological development

The effects of prenatal maternal stress on the offspring often extend further than to perinatal outcomes. Prematurity and low birthweight, especially for gestational age, are known to increase the risk of several illnesses and neurodevelopmental problems, particularly concerning cognition, attention, and neuromotor functioning (Hack, Klein, & Taylor, 1995; Räikkönen & Pesonen, 2009; Torche & Echevarria, 2011). Birthweight has also been found to predict MRI-derived measures of brain development, such as cortical thickness, surface

area, and brain volumes (Walhovd et al., 2012), and preterm birth has been associated with a wide array of psychiatric morbidity, including psychotic or bipolar disorders, autism and ADHD (D'Onofrio et al., 2013). Despite being risk factors for a variety of impairments later in development, offspring size at birth and length of gestation are merely rough indicators of the fetal environment and lend little to the understanding of causal relationships as such (Gluckman & Hanson, 2004). However, an essential underlying contributory factor that has been shown to affect both birth outcomes and later child development could, expressly, be stress experienced by the pregnant mother.

Research on the associations between prenatal maternal stress and offspring outcomes has provided ample evidence of detrimental effects. Studies have shown an increased risk of emotional and behavioral problems, such as anxiety (O'Connor et al., 2002), externalizing problems (Van den Bergh & Marcoen, 2004) and antisocial behavior (Rice et al., 2010). Delay in mental and motor development have been reported (Buitelaar, Huizink, Mulder, de Medina, & Visser, 2003; Huizink, Robles, Mulder, Visser, & Buitelaar, 2003) as well as poorer cognitive skills (Huizink, de Medina, Mulder, Visser, & Buitelaar, 2002; Laplante et al., 2004). Exposure to maternal stress *in utero* has also been associated with fearfulness and negative temperament in the offspring (Bergman, Sarkar, O'Connor, Modi, & Glover, 2007; de Weerth, van Hees, & Buitelaar, 2003). Moreover, maternal psychosocial stress, as measured by both cortisol levels and the subjective experience of stress, has been shown to affect the functioning of the infant's hypothalamic pituitary adrenal (HPA) -axis and thereby stress regulation (Davis, Glynn, Waffarn, & Sandman, 2011; Glover, O'Connor, & O'Donnell, 2010). In animal studies, changes in hippocampal development and regulation of the HPA axis (stress reactivity), impaired cognitive function (learning) and deficits in attention (Schneider, Moore, Kraemer, Roberts, & DeJesus, 2002; Schneider, 1992) have also been noted. Moreover, changes in social behavior (withdrawal) and motor behavior (Schneider, 1992), as well as alterations in the sleep-wake cycle (Maccari et al., 2003) have been found.

The occurrence of the effects may be influenced by the characteristics of the offspring, such as sex. Sex of the offspring is hypothesized to interact with stress induced maternal physiological changes through different placental functioning (Bronson & Bale, 2014). In males, exposure to prenatal maternal stress is more likely to influence cognitive aspects, such as learning (Zagron & Weinstock, 2006), memory (Schulz et al., 2011) or attention

(O'Connor et al., 2002; Van den Bergh & Marcoen, 2004). In females, the effects are more likely to present as increased emotional symptoms, such as anxiety or affective disorders (Buss et al., 2012). Nevertheless, in some studies, no sex differences have been found (Rice et al., 2010). Overall, there appears to be great variation across children in how severe as well as persistent the effects are, which seems to be due to the interplay of the vast number of factors affecting the outcome.

1.1.3 The timing of stress

The majority of studies in which the timing of stress has been taken into account have shown significant differences in the effects according to the pregnancy trimester (Class et al., 2014; Glynn et al., 2001; Rodriguez & Bohlin, 2005; Weinstock, 2008). The most critical time for stress to cause adverse effects varies depending on the outcome measured. Prenatal maternal stress experienced early in pregnancy has been repeatedly associated with a higher risk of preterm birth and smaller size at birth (Glynn et al., 2001; Torche & Kleinhaus, 2012; P. Zhu et al., 2010), discussed above in more detail. Exposure to high levels of subjective prenatal stress in the 1st trimester has also been associated with smaller head circumferences (Dancause et al., 2011). Maternal stress caused by a natural disaster in the 1st and 2nd pregnancy trimesters, but not in the 3rd, has been associated with poorer cognitive outcome in children at two years of age (Laplante et al., 2004). High stress caused by daily hassles in early-pregnancy has been associated with impaired mental and psychomotor development in 8-month-olds (Buitelaar et al., 2003), and pregnancy-specific anxiety at 13 weeks of gestation has been associated with poorer mental development in 12-month-olds (Davis & Sandman, 2010). Also, the risk of developing schizophrenia has been associated with 1st trimester stress caused by the death of a close relative (Khashan et al., 2008). None of these associations were significant for mid- or late-pregnancy stress. All results were obtained after controlling for confounding factors, such as the child's sex, birthweight and socioeconomic status.

In mid-pregnancy, strong fear of giving birth has been associated with delayed mental and psychomotor development at 8 months of age (Buitelaar et al., 2003). The association was not significant for fear earlier or later in pregnancy. Specific findings concerning prenatal stress during mid-pregnancy are scarce, but anxiety during the second trimester has been

associated with reductions in gray matter volume in 6–9-year-olds (Buss, Davis, Muftuler, Head, & Sandman, 2010), impaired cognitive and language abilities in 2- and 5½-year-olds (Laplante et al., 2008; Laplante et al., 2004) and increased externalizing problems and anxiety in 8–9-year-olds (Van den Bergh & Marcoen, 2004). None of these associations, either, were significant for early- or late-pregnancy anxiety.

While much evidence points to early through mid-pregnancy being the most critical time for stress-related fetal effects, other data indicates late gestation to be the most influential. Davis and colleagues (2007) found that prenatal maternal anxiety and elevated cortisol levels only at 30–32 weeks of gestation, but not earlier in pregnancy, were predictive of negative reactivity in 8-week-old infants. O'Connor, Heron, Golding, Beveridge and Glover (2002) and O'Connor, Heron, Golding, Glover and the ALSPAC Study Team (2003) assessed maternal anxiety and depression at 18 and 32 weeks of pregnancy and found associations between prenatal anxiety and children's behavioral/emotional problems at 4 and 6½ years of age. The results were strongest for late-pregnancy anxiety and especially regarding hyperactivity/inattention in boys. More recent findings from the same cohort have shown lasting effects on emotional and behavioral problems in 4–13-year-old children – however, with no significant differences between maternal symptoms at 18 and 32 weeks of pregnancy (O'Donnell, Glover, Barker, & O'Connor, 2014).

When considering the timing of stress exposure clear cut-off points are difficult to establish. With the exception of acute stress that starts abruptly, both the beginning and end of experiencing stress are usually indistinct and gradually changing. However, regardless of the gestational timing, the consequences of prenatal stress exposure have been shown to be long-lasting, at most, down to the grandchild generation (Matthews & Phillips, 2011; Ward et al., 2013), which raises the question of how the effects are mediated.

1.2 Mechanisms

Research in the past years has focused increasingly on the mechanisms underlying the transmission of prenatal stress-induced effects on the offspring. The specific pathways have yet to be confirmed, but "fetal programming" is thought to play a central role (D. J. Barker, 2007). The Developmental Origins of Health and Disease (DOHaD) –hypothesis was first

coined by Barker (1998) to describe the persisting changes in development that may take place as a result of environmental stimuli *in utero*. With the purpose of adapting to the future environment (Glover, 2011), the growth and development of the fetus may be permanently altered by environmental conditions such as undernutrition (D. J. Barker, 1998). Barker, Osmond, Golding, Kuh and Wadsworth (1989) discovered an association between low birthweight and increased risk of coronary heart disease in adulthood. The DOHaD-hypothesis has also been widely corroborated in relation to the Dutch Hunger Winter (Heijmans et al., 2008; Roseboom, Painter, van Abeelen, Veenendaal, & de Rooij, 2011; Schulz, 2010). Exposure to prenatal maternal undernutrition during the famine in 1944–1945 led to smaller offspring size at birth, but it also predisposed to cardiovascular disease in adulthood independent of birthweight (Painter, Roseboom, & de Rooij, 2012). The outcomes revealed an association between 2nd and 3rd trimester undernutrition and lower birthweight, whereas children exposed in the 1st trimester were born with normal birthweights, but had a heightened risk of obesity later in life. Prenatal famine exposure was also found to increase the risk of schizophrenia (Susser et al., 1996), antisocial personality disorder (Neugebauer, Hoek, & Susser, 1999) and declined cognitive ability later in life (de Rooij, Wouters, Yonker, Painter, & Roseboom, 2010). The findings supported the view that the influence of the environmental stimulus is dependent on the timing of exposure, and that the programming effects may become visible even after long delay as the relevant physiological structures become active.

In recent years, focus on stress-related mechanisms has broadened onto psychological factors. Emerging evidence points to similar programming effects to apply to psychological conditions, such as prenatal stress and anxiety (Van den Bergh, Mulder, Mennes, & Glover, 2005; Wadhwa, 2005). The effects appear to be mediated through several mechanisms on epigenetic, physiological and psychological levels, which will be briefly reviewed next.

1.2.1 Physiological pathways and epigenetics

On a physiological level, stress is suggested to affect the expecting mother's HPA-axis and to increase the secretion of glucocorticoids, most importantly cortisol (Kudielka & Kirschbaum, 2005). Cortisol is a steroid hormone involved in a wide range of physiological processes, including metabolism, immune control, memory formation and stress response

(Bellavance & Rivest, 2014; Munck, Guyre, & Holbrook, 1984). Prenatal maternal stress has been found to increase maternal cortisol levels in both animal (Barbazanges, Piazza, Le Moal, & Maccari, 1996; Schneider, Roughton, Koehler, & Lubach, 1999) and human studies (Diego et al., 2006; Sandman, Wadhwa, Chicz-DeMet, Dunkel-Schetter, & Porto, 1997), although the association appears to be weaker in humans and unlikely to be the sole mediator of stress-induced effects (Hompes et al., 2013; O'Donnell, O'Connor, & Glover, 2009).

The placenta acts as a central moderator of fetal exposure to maternal factors (Jansson & Powell, 2007). Most of the maternal cortisol is metabolized into its inactive form cortisone as it crosses the placenta by the enzyme 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD-2), which thus regulates the passage of cortisol into the fetal compartment (Painter et al., 2012). As maternal cortisol levels increase two- to four-fold throughout pregnancy (Sandman et al., 2006), the activity of the placental enzyme 11β-HSD-2 also increases (Murphy & Clifton, 2003). However, towards the end of pregnancy, the activity of the placental enzyme drops and higher levels of cortisol are allowed into fetal blood circulation (Murphy, Smith, Giles, & Clifton, 2006). Growing evidence suggests that maternal stress may lead to a down-regulation of 11β-HSD-2 (Mairesse et al., 2007; O'Donnell et al., 2012). Despite the fetal HPA-axis becoming functional from mid-gestation (Gitau, Fisk, Teixeira, Cameron, & Glover, 2001), the dysregulation of the maternal HPA-axis, including the decrease in placental enzymes, may cause fetal exposure to cortisol to be further elevated reaching excessive levels (Gelman, Flores-Ramos, López-Martinez, Fuentes, & Grajeda, 2015).

The regulation of appropriate levels of cortisol with respect to critical developmental windows is crucial, as cortisol is necessary for fetal growth, maturation, immune function and brain development, including the areas responsible for the regulation of emotion and cognitive function (Davis & Sandman, 2010; Kudielka & Kirschbaum, 2005). Conversely, excessive fetal exposure to cortisol has been associated with detrimental offspring outcomes (Buss et al., 2012; Davis & Sandman, 2010), and reduced placental enzyme activity has been postulated to modify the neurological structure and behavior of the offspring (O'Donnell et al., 2009). Reduced 11β-HSD-2 activity has also been discovered in relation to preterm birth (Kajantie, Dunkel, Turpeinen, Stenman, & Andersson, 2006) and intrauterine growth restriction (Dy, Guan, Sampath-Kumar, Richardson, & Yang, 2008), which have, sequentially, been associated with adverse long-term consequences (Aarnoudse-Moens,

Weisglas-Kuperus, van Goudoever, & Oosterlaan, 2009; Geva, Eshel, Leitner, Valevski, & Harel, 2006; Räikkönen et al., 2008). In addition to cortisol-related effects, other suggestions for stress-induced mechanisms mediated by the placenta include reductions in fetoplacental blood flow – which have been associated with restricted fetal growth – (Helbig, Kaasen, Malt, & Haugen, 2013) and increases in proinflammatory cytokine levels (Coussons-Read, Okun, Schmitt, & Giese, 2005) – which have been associated with pre-eclampsia (Azizieh, Raghupathy, & Makhseed, 2005) and premature delivery (Makhseed et al., 2003).

The mediating role of the placenta also appears to be controlled by epigenetic mechanisms – changes in gene expression mediated by DNA methylation, post-translational modification of histones or noncoding RNA that do not involve alterations in DNA sequence (Monk, Spicer, & Champagne, 2012; Reynolds, Jacobsen, & Drake, 2013). In addition to leading to elevated fetal cortisol levels as described above, prenatal maternal stress may modify the gene activity in placental tissues (Monk et al., 2012; Reynolds et al., 2015). Prenatal stress has been associated with altered DNA methylation in the 11β-HSD-2 gene promoter and, to a lesser extent, in the fetal brain (Jensen Peña, Monk, & Champagne, 2012). Changes in the regulation of glucocorticoid receptor gene expression have been found in the offspring of stressed, depressed or anxious women (Hompes et al., 2013; Oberlander et al., 2008; Reynolds et al., 2015). These changes have, in turn, been associated with increased cortisol stress responses in infancy (Oberlander et al., 2008). Epigenetic mechanisms are thought to extend to the maturation of fetal organs including the brain, and to mediate the influence of environmental stimuli on genetically programmed development (Bock, Rether, Gröger, Xie, & Braun, 2014). Epigenetics may also be responsible for transgenerational inheritance through alterations persisting in the germline (Crews et al., 2012; Kapoor, Petropoulos, & Matthews, 2008).

1.2.2 Psychologically induced pathways and confounding factors

Alongside direct physiological pathways, stress affects the mother psychologically. Experiencing psychosocial stress has been shown to increase unhealthy behaviors during pregnancy (Dunkel Schetter & Lobel, 2010). Smoking, higher fat/calorie diets and less frequent exercising have been generally noted in relation to stress (Hurley, Caulfield, Sacco, Costigan, & Dipietro, 2005; Ng & Jeffery, 2003; Teegarden & Bale, 2008) – all of which, in

turn, have been associated with less than optimal child outcomes in pregnant women (E. D. Barker, Kirkham, Ng, & Jensen, 2013; Bhagat, Fortna, & Browning, 2015; Mei-Dan et al., 2014; Weissgerber, Wolfe, Davies, & Mottola, 2006). Unhealthy diet and exercise habits have also been linked to a higher maternal body weight as measured by the body mass index (BMI), which has been associated with fetal complications (Aune, Saugstad, Henriksen, & Tonstad, 2014; Khashan & Kenny, 2009).

Experiencing prenatal stress has implications through the mother's emotions and behavior not only for the gestational period, but also postnatally. Mothers' pre- and postnatal stress experiences have been found to be correlated (Pesonen, Räikkönen, Strandberg, & Järvenpää, 2005), and anxiety during pregnancy has been shown to predict postpartum anxiety and depression (Heron, O'Connor, Evans, Golding, & Glover, 2004). Successively, postpartum maternal psychological problems have been associated with adverse outcomes in children, including emotional and conduct problems (O'Connor et al., 2003), behavioral disturbances, difficulty sustaining attention and altered mother-child attachment (Dawson, Ashman, & Carver, 2000). The stability in individual differences concerning mood and anxiety has been found to be notable (Heron et al., 2004), indicating the probability of exposure to maternally mediated risk factors to be long-lasting. Furthermore, considering that prenatal maternal stress caused by partner-related relationship strain has been suggested the most predictive form of stress for child outcomes (Bergman et al., 2007), clinically relevant maternal stress is also likely to be correlated with paternal levels of stress. Postnatal paternal well-being, in turn, has also been shown to affect the emotional and behavioral development of the offspring (Ramchandani, Stein, Evans, O'Connor, & ALSPAC Study Team, 2005).

1.3 Attention deficit hyperactivity disorder

1.3.1 Clinical expression and prevalence

Attention deficit hyperactivity disorder (ADHD) is a neuropsychiatric disorder characterized by symptoms of inattention, hyperactivity and impulsivity. The clinical expression of ADHD varies greatly, including the severity of the symptoms and the level of affliction. The diagnostic criteria are presented in Table 1. ADHD is the most common neurobehavioral disorder among children (Wolraich et al., 2011). The worldwide prevalence of ADHD

among children and adolescents was estimated to be 5.29 % in a comprehensive meta-analysis (Polanczyk, de Lima, Horta, Biederman, & Rohde, 2007) and 5.9-7.1 % in another (Willcutt, 2012). Despite the increased number of ADHD diagnoses in the past years (Visser et al., 2014), no evidence of an actual increase in the prevalence of ADHD over the past three decades was found in a recent meta-analysis (Polanczyk, Willcutt, Salum, Kieling, & Rohde, 2014), indicating the variability in the prevalence estimates to be largely due to differences in study methods and especially in diagnostic procedures. While, in some studies, the prevalence of ADHD has been found to vary across countries (Hinshaw et al., 2011), no significant differences between continents have been found (Wolraich et al., 2003).

Table 1. Subtypes of ADHD. Diagnostic criteria include six or more symptoms that are present in two or more settings and that interfere with, or reduce the quality of, functioning (American Psychiatric Association, 2013).

Type	**Symptoms**
Inattentive	• Fails to give close attention to details or makes careless mistakes. • Has difficulty sustaining attention. • Does not appear to listen. • Struggles to follow through on instructions. • Has difficulty with organization. • Avoids or dislikes tasks that require sustained mental effort. • Loses things. • Is easily distracted. • Is forgetful in daily activities.
Hyperactive / Impulsive	• Fidgets with hands or feet or squirms in chair. • Has difficulty remaining seated. • Runs about or climbs excessively. Difficulty engaging in activities quietly. • Is “on the go” or acts as if “driven by a motor”. • Talks excessively. • Blurts out answers before questions have been completed. • Difficulty waiting or taking turns. • Interrupts or intrudes upon others.
Combined	Enough symptoms of both inattention and hyperactivity/impulsivity.

The incidence of ADHD differs across several sociodemographic factors. ADHD is significantly more common in boys than girls, with rates of 15.1 % and 6.7 %, respectively, in the USA (Visser et al., 2014) and 8.5 % in total with a male-female ratio of 5.7:1 in Finland (Smalley et al., 2007). However, girls are frequently underdiagnosed (Quinn, 2005), which might be partly due to sex differences in the development and symptoms of ADHD. Compared to boys, the symptoms in girls are often less "visible" – girls tend to have lower levels of hyperactivity and externalizing problems, but higher rates of inattention, intellectual impairment and internalizing behaviors (Gaub & Carlson, 1997; Gershon, 2002). In addition to sex differences, the incidence of ADHD varies by family factors. Children of lower socioeconomic status (SES) are more likely to develop ADHD than children of higher SES (Merikangas et al., 2010). Low maternal age and caesarean section as mode of birth have also been identified to increase the risk of ADHD (Valdimarsdottir, Hrafnsdottir, Magnusson, & Gudmundsson, 2006). Moreover, being firstborn has been associated with an almost doubled risk of ADHD compared to other birth orders (Marin et al., 2014).

The occurrence and severity of ADHD symptoms appear to be highest between ages 5 and 10, and decrease by age leading to smaller prevalence rates in later childhood and adolescence than in young children (Charach et al., 2011). ADHD is most often diagnosed at 7 years of age, but children with more severe symptoms are often diagnosed earlier, and the diagnostic criteria can be applied to children from 4 years up (Visser et al., 2014; Wolraich et al., 2011). The symptoms vary both between and within individuals, but follow generally a similar pattern of course – hyperactivity and impulsivity tend to diminish more and earlier compared to inattentiveness (Biederman, Mick, & Faraone, 2000). Despite the symptoms peaking in school-age, screening for signs of ADHD in younger children is warranted as symptoms of inattention that are absent at an early age are also unlikely to develop later (Rietveld, Hudziak, Bartels, van Beijsterveldt, & Boomsma, 2004).

Although the symptoms of ADHD often diminish with age, up to 80 % of children diagnosed with ADHD still have symptoms in adulthood (Faraone, Sergeant, Gillberg, & Biederman, 2003). By causing problems with executive function, the disorder may affect all aspects of an individual's life leading to hardship both on a personal as well as a communal level (Hinshaw, 2002). The degree of comorbidity is high, particularly with oppositional defiant disorder, anxiety disorder and learning disorders (Biederman, Newcorn, & Sprich, 1991;

Jensen, Martin, & Cantwell, 1997). From a public health perspective, ADHD is thus of major concern.

1.3.2 Etiology

The etiology behind ADHD is extremely complex and largely yet unknown. In addition to a strong genetic component of up to 79 % heritability (Lichtenstein et al., 2010), several environmental risk factors seem to play a role in the onset of ADHD. Environmental factors have been suggested to play a significant role in determining child outcomes, even if the primary causes of the development of ADHD appear to lie in the strong biological disposition of the disorder (Barkley, 2005). Common to most, if not all, known environmental causes is exposure in early developmental stages, i.e. in the fetal or neonatal period (Banerjee, Middleton, & Faraone, 2007). Birth outcomes, such as preterm birth (Anderson et al., 2011; Lindström, Lindblad, & Hjern, 2011), low birthweight and being SGA (Heinonen et al., 2010; Strang-Karlsson et al., 2008), have been associated with later ADHD symptoms. Both preterm and early term birth were found to increase the risk of ADHD in a large (n > 1,100,000) Swedish cohort study, where the researchers also noted a dose-response effect (Lindström et al., 2011). Low birthweight has also been independently associated with all subtypes of ADHD symptoms in twin-studies (Pettersson et al., 2015), and preterm birth has been associated with subsequent ADHD symptoms similarly in twin- (Lindström et al., 2011) as well as cohort studies (Anderson et al., 2011), indicating a causal relationship of prenatal adversity with ADHD. Furthermore, maternal viral and genitourinary infections during pregnancy as well as pre-eclampsia have been associated with increased risk of child ADHD (Arpino, Marzio, D'Argenzio, Longo, & Curatolo, 2005; Mann & McDermott, 2011). Also, high maternal pre-pregnancy BMI has been associated with higher levels of ADHD symptoms in the offspring (Rodriguez et al., 2007).

Maternal risk behaviors during pregnancy have received attention as potential contributors to offspring ADHD risk (Linnet et al., 2003). Animal studies have shown prenatal nicotine exposure to lead to increased hyperactivity in the offspring (J. Zhu et al., 2012), and most human studies similarly indicate significant associations between maternal smoking and ADHD symptoms in the children (Kovess et al., 2014; Linnet et al., 2005; J. Zhu et al., 2014). Maternal alcohol consumption during pregnancy has been associated with increased

offspring ADHD in some studies (Mick, Biederman, Faraone, Sayer, & Kleinman, 2002), but not in others (Hill, Lowers, Locke-Wellman, & Shen, 2000). Maternal dietary factors, such as nutritional deficiencies or surpluses, as well as caffeine intake, have been researched in relation to ADHD, but only the ingestion of high amounts of licorice has been associated with attention problems in the offspring (Räikkönen et al., 2009); no other maternal diet - related increases in ADHD risk have been identified (Loomans et al., 2012; Thapar, Cooper, Eyre, & Langley, 2013). However, *in utero* exposure to environmental toxins, like lead or organic pollutants, has been related to ADHD symptoms in the child (Nigg et al., 2008; Sagiv et al., 2010). Environmental risk factors appear to affect fetuses of both sexes equally, as the sex differences noted have been minimal (Silva, Colvin, Hagemann, & Bower, 2014).

Maternal risk factors also include the mother's psychological factors. Maternal ADHD symptoms, as well as hostile parenting behavior, have been associated with child ADHD symptoms in unrelated dyads, with genetic influences ruled out (Harold et al., 2013). Strong associations have also been found between negative parent-child relationships and ADHD symptoms in the child (Deault, 2010). However, causal relationships are difficult to establish, as child ADHD symptoms and more difficult temperamental traits may also affect the parent-child relationship in a negative manner (Deault, 2010; Johnston & Jassy, 2007).

On a neurobiological level, children with ADHD have been found to have dysregulated HPA-axis functioning (Ma, Chen, Chen, Liu, & Wang, 2011), and smaller white and gray matter volumes in several areas of the brain, including the frontal regions, compared to children without ADHD (Castellanos et al., 2002; Valera, Faraone, Murray, & Seidman, 2007). Also, altered neurotransmitter functioning has been noted in ADHD children (Aguiar, Eubig, & Schantz, 2010). Interestingly, the neurobiological alterations witnessed in children exhibiting ADHD symptoms appear to be similar to the ones associated with prenatal maternal stress exposure (Buss et al., 2010; Pallarés & Antonelli, 2014).

1.4 Psychological well-being of the mother and offspring ADHD

The association between prenatal maternal stress and ADHD symptoms in the offspring has received growing attention over the past years. Due to the broad definition of stress and the notable overlap with psychiatric symptoms, research on associations between prenatal

anxiety and depression and offspring ADHD may also prove relevant in providing insight into the effects of prenatal stress on child ADHD symptoms. The main outcomes concerning the associations between prenatal psychiatric symptoms and child attention problems will be briefly summed up next. Subsequently, previous studies on prenatal maternal stress and offspring ADHD risk will be reviewed.

1.4.1 Prenatal maternal psychiatric symptoms and offspring ADHD

Prenatal maternal anxiety and depression are highly comorbid disorders (Pollack, 2005) and comprise several shared symptoms (American Psychiatric Association, 2013). The disorders are strongly intertwined with experiencing psychological stress and may be further elevated in response to stress (Maccari et al., 2003). Studies on anxiety and depression often focus on symptoms as opposed to full diagnoses (Julian, 2011), which posits them closer to the generic field of "stress". Research on associations between prenatal maternal anxiety or depression and offspring ADHD symptoms is scarce. However, the few studies conducted have provided supportive evidence of significant associations and have mainly applied reasonably well-designed study settings.

In a large (n = 7,824), prospective, population-based study, O'Connor, Heron, Golding, Beveridge and Glover (2002) and O'Connor, Heron, Golding, Glover and the ALSPAC Study Team (2003) found anxiety in late pregnancy to predict hyperactivity and inattention symptoms in 4-year-old boys and 6½-year-old boys and girls. A similar result was found in a smaller (n = 143) prospective study by Van den Bergh and Marcoen (2004), who found that maternal anxiety in mid-pregnancy was a significant independent predictor of child ADHD symptoms at 8–9 years of age. Postnatal maternal well-being was controlled for in both studies. Moreover, both maternal anxiety and depressive symptoms were independently associated with child attention problems in 3–4-year-olds in a study comprising two large cohorts (Van Batenburg-Eddes et al., 2013). In one of the cohorts (Generation R) the association was no longer significant after controlling for postnatal maternal symptoms. In the other cohort (Avon Longitudinal Study of Parents and Children; ALSPAC), also prenatal paternal depression was associated with an increased risk of attention problems in the child. Interestingly, the researchers noted that prenatal maternal and paternal depression and anxiety had only marginally different effects on child attention problems. Furthermore, in

two other prospective cohort studies, prenatal maternal anxiety was associated with increased hyperactivity/inattention problems in 5-year-old boys (Loomans et al., 2011) and with persistent attention problems in 5- and 14-year-old children (Clavarino et al., 2010). Loomans and colleagues (2011) found child sex to significantly moderate the relation between prenatal anxiety and child hyperactivity/inattention problems in 3,777 participants after adjusting for covariates including a measure of current maternal emotional distress that was significantly correlated with child ADHD symptoms. Clavarino and colleagues (2010) also found a gender difference in 3,982 children at five years of age, but not in adolescence. The researchers noted a cumulative effect for maternal anxiety over time: maternal anxiety exposure both prenatally and up to age 5 was most predictive of child attention problems. Moreover, the effects may even be detectable from infancy onwards, as pregnancy anxiety has been associated with decreased attention regulation in 3-month-olds, and both pregnancy anxiety and perceived stress have been related to decreased attention regulation in 8-month-olds after controlling for confounding factors, including postnatal maternal stress (Huizink et al., 2002).

1.4.2 Prenatal maternal stress and offspring ADHD

Although maternal stress during pregnancy has been recognized as a noteworthy factor contributing to developmental outcomes in children, its association with ADHD has only been researched in a limited number of studies. Previous studies have varied greatly in assessment methods of both prenatal stress and ADHD, sample composition (population based vs. clinical) and size, as well as controlling of covariates. To my knowledge, only 11 studies to date have focused specifically on the association between prenatal maternal stress and child ADHD symptoms. Of those, significant associations were found in ten – in only one study offspring ADHD was concluded to be solely linked to genetic inheritance (Rice et al., 2010). Timing differences have been considered in six studies, of which significant differences in exposure times were only found in one (Class et al., 2014), although stronger associations for certain time points were noted in three more (Grizenko, Shayan, Polotskaia, Ter-Stepanian, & Joober, 2008; Li, Olsen, Vestergaard, & Obel, 2010; Rodriguez & Bohlin, 2005). Sex differences have been researched in three studies – in two, the associations were significant only in boys (Li et al., 2010; Rodriguez & Bohlin, 2005), and in one, the associations were significant in both sexes (Ronald et al., 2011). A prospective approach has

been applied in four studies, of which two actively involved participants (Rodriguez & Bohlin, 2005; Ronald et al., 2011) and two were solely registry-based (Class et al., 2014; Li et al., 2010), whereas all others have relied on retrospective reports of maternal stress. The main findings of prior research on the association between prenatal maternal stress and child ADHD symptoms are reviewed below. An overview of the studies is presented in Table 2, which is organized according to the level of specificity of the study design, starting with the studies reporting significant associations.

In both of the prospective studies actively involving participants, confirming results for the association between prenatal stress exposure and an increased risk of child ADHD were found. Rodriguez and Bohlin (2005) recruited 208 dyads to investigate whether smoking and prenatal maternal stress predict ADHD symptoms in 7-year-olds. The researchers found prenatal stress exposure to be independently associated with ADHD symptoms for the whole sample and in boys after controlling for sociodemographic factors. The association was strongest for stress at week 10 of pregnancy. In girls, no significant association was found. However, the lack of controlling for maternal ADHD and postnatal stress measures limits the interpretation of the results. In the other study, Ronald and colleagues (2011) examined whether prenatal maternal stress predicts behaviors characteristic of autism and ADHD in early childhood. They recruited a large community sample (n = 2,900) and evaluated the children at 2 years of age. The results showed a significant association between maternal stress during pregnancy and ADHD behaviors in both sexes after controlling for several confounding factors, including autistic traits. Interestingly, this association was already significant in 2-year-old children. The study design included a postnatal covariate of maternal mood, but the measurement only took place within days of giving birth, and failed to include assessments later on.

Of the longitudinal registry-based studies, moderating effects of the sex of the child were found in one study, and significantly differing results based on the timing of the stress exposure, in another. In both studies, information on both bereavement and child ADHD was obtained solely from national registries. Li and colleagues (2010) used a large Danish cohort (n > 1,000,000) to investigate the association between maternal bereavement stress and offspring ADHD, defined as the death of a close relative and first-time ADHD hospitalization or first-time ADHD medication after three years of age, respectively. The researchers found boys to have a 72 % increased risk of ADHD in cases where their mothers

were bereaved by the unexpected death of a child or a spouse. In girls, no associations were found. The findings also suggested exposure to severe stress in late pregnancy to have more prominent effects than in early pregnancy. Despite the large sample size, not all children with ADHD symptoms are likely to be hospitalized or to receive medication, thus presenting a limitation to the study. Recently, Class and colleagues (2014) investigated the effects of preconception, prenatal and early postnatal maternal bereavement stress, caused by the death of a first-degree relative, on the risk of child psychopathology. A significant association between prenatal stress and offspring ADHD was found for 3rd trimester exposure, but not earlier. The strengths of the study included using a large population database (n > 700,000) and controlling for several confounding factors. However, the researchers failed to inspect the possible confounding effects of postnatal stress exposure. Also, using an objective binary measure of stress is coarse and unlikely to adequately reflect maternal experiences of stress.

Six other studies have been generally smaller in size, and – apart from one – have not assessed sex or timing differences as moderators of stress-induced effects on the offspring. Grizenko, Shayan and colleagues (2008) recruited a clinical sample of 203 children and evaluated their ADHD symptoms at 6–12 years of age. The researchers found a significant association between prenatal stress and child ADHD symptoms, and noted that exposure to moderate or severe stress during pregnancy was associated with increased severity of ADHD symptoms. Increased stress in the third trimester was found to be correlated with more severe ADHD symptoms in the child, and the association was suspected to be partly mediated by probable postnatal stress exposure. Unfortunately, the study setting did not allow for controlling for postnatal environmental factors. In a more recent study, Grizenko, Fortier and colleagues (2012) used an intra-familial design to investigate retrospectively whether mothers experienced more stress while pregnant with their ADHD-children as compared to their non-ADHD-siblings, and to examine gene-environment interactions by genotyping the children. Seventy one sibling pairs aged 6–12 were assessed for ADHD symptoms, and the mothers were divided into two categories according to their stress levels (no/mild vs. moderate/severe/extreme stress). The researchers found a significant association between higher levels of maternal stress and ADHD symptoms in the child after controlling for multiple covariates, including postnatal stress. The results also showed a significant interaction between prenatal stress and child DRD4 7/7 genotype, suggesting the association between prenatal maternal stress and child ADHD symptoms to be moderated by genotype.

To examine the association between prenatal psychosocial stress and child ADHD at 7–18 years of age, Motlagh and colleagues (2010) measured the family's level of stress severity in 117 participants. The results showed both severe levels of psychosocial stress and heavy maternal smoking to be independently associated with child ADHD. The presence of prenatal marital stressors was associated with greater ADHD severity compared to the absence of marital stress. In a study on the role of self-perceived distress during pregnancy for unfavorable childhood outcomes, Martini, Knappe, Beesdo-Baum, Lieb and Wittchen (2010) found a significant association between prenatal stress and offspring ADHD ever diagnosed in 992 participants at 14-27 years of age, after adjusting for maternal depressive disorders after birth. Kim and colleagues (2009) used a Korean community sample (n = 2,673) of 6–18-year-old students, and investigated whether perinatal and familial risk factors were associated with offspring ADHD. The researchers included both full syndrome and sub-threshold ADHD to examine whether milder forms of ADHD are similarly associated with the same risk factors. The findings showed prenatal maternal stress to be significantly associated with full syndrome ADHD, and as the only perinatal risk factor, also with subthreshold ADHD. In a recent study, Park and colleagues (2014) compared the combined subtype of ADHD to the inattentive subtype in terms of several risk factors, including prenatal maternal stress. A total of 649 children aged 6–15 years participated. Severe maternal stress during pregnancy was found to be significantly associated with both the combined and the inattentive subtype of ADHD.

While the majority of studies have shown significant associations between maternal stress and offspring risk of ADHD, one has presented contradicting results. Rice and colleagues (2010) compared genetically related and unrelated (conceived through *in vitro* fertilization) mother-child dyads with respect to the link between prenatal stress and offspring outcome at 4–10 years of age. The analyses yielded a significant association between maternal stress and offspring ADHD only in the related dyads but not in the unrelated ones, suggesting the link to be due to inherited factors. However, despite the strengths of using a non-dichotomous measure of stress and considering timing differences in stress exposure, this study had a relatively small sample size (n = 474) and relied on retrospective reports of prenatal stress. Excluding ADHD (due to the lack of a significant association), the associations between prenatal stress and other child outcomes (anxiety, antisocial behavior) were adjusted for postnatal maternal anxiety/depression at the time of child symptom evaluation. This proved important, as postnatal maternal well-being was found to

significantly mediate the association between prenatal maternal stress and child anxiety symptoms.

Taken together, most evidence suggests that prenatal maternal stress is associated with an increased risk of child ADHD. The effects have become evident with different time points of stress exposure, although the strongest associations have mainly been found for late pregnancy stress (Class et al., 2014; Li et al., 2010). Where sex differences have been examined, the associations have usually been strongest in boys (Li et al., 2010; Rodriguez & Bohlin, 2005). The effects have been noted in children of all ages, from two years of age (Ronald et al., 2011) to adulthood (Li et al., 2010). However, the generalizability of the findings of several of the studies has been restricted by methodological shortcomings, and unfortunately, none of the studies have adequately controlled for postnatal maternal stress, which is known to be an important confounding factor for child outcomes (O'Connor et al., 2003; Rice et al., 2010). Furthermore, the potential confounding effects of postnatal paternal stress on the associations between prenatal maternal stress and child ADHD risk have not been considered in any previous studies.

Table 2. Previous research on the association between prenatal maternal stress and offspring ADHD symptoms.

Study	**Independent variable** Type of maternal stress	Measures	Timing (Pregnancy week)	**N**	**Dependent variable** Measures	Timing (Age of child in years)	**Covariate** Maternal postnatal well-being	**Results** Association with ADHD symptoms
Rodriguez & Bohlin (2005)	Prenatal stress	PSS, 10 Q	PS 1: 10 2: 12 3: 20 4: 28 5: 32 6: 36	208	DSM-IV	7	No	Significant, especially in boys; strongest for week 10 exposure
Ronald et al. (2011)	Major life stress events	Life stress inventory, 10 Q	PS 1: 18 2: 34	2,868	CBCL	2	Only at birth	Significant in both sexes
Li et al. (2010)	Bereavement stress	Death of a close relative: yes/no	RB 0-12 13-24 24-birth	1,015,912	ICD-10: F90, use of ADHD medication	3–19	No	Only significant in boys, only for death of child or partner; strongest for 3rd trimester exposure
Class et al. (2014)	Bereavement stress	Death of a first-degree relative: yes/no	RB 0-12 13-24 25-birth	738,144	ICD-10: F90	2 <	Bereavem. stress	Only 3rd trimester exposure significant
Grizenko et al. (2008)	Stressful life events	5-point Likert scale (KMGQ)	RS 1st trimester 2nd trimester 3rd trimester	203	DSM-IV-R, DISC-IV, CBCL, CGI-P	6–12	No	Significant dose-response effect; strongest for 3rd trimester exposure

Grizenko et al. (2012)	Stressful life events	5-point Likert scale (KMGQ)	RS	142	DSM-IV, CBCL, CGI-P	6–12	Postnatal stress	Significant
Park et al. (2014)	Prenatal stress	Severe stress: yes/no	RS	649	ADHD-RS, DBDS, CBCL	6–15	Postpartum depression	Significant
Motlagh et al. (2010)	Psychosocial stress	5-point ordinal scale, MSRPFED	RS	117	SADS-PL, DuPaul-Barkley	7–18	No	Significant
Kim et al. (2009)	Prenatal stress	Structured questionnaires	RS	2,673	DISC-IV	6–18	No	Significant
Martini et al. (2010)	Self-perceived distress	4-point Likert scale, 1 Q	RS	992	DSM-IV	14–27	Depressive disorder	Significant
Rice et al. (2010)	Prenatal stress	11-point Likert scale, 1 Q	RS 0-16 17-30 31-40	474	Du Paul - questionnaire	4–10	Not for ADHD	Only significant in related dyads

PS = prospective, Q = question, RB = registry-based, RS = retrospective

ADHD-RS (ADHD Rating Scale), CBCL (The Child Behavior Checklist), CGI-P (Conners' Global Index, Parent Version), DBDS (the Disruptive Behavioral Disorder Rating Scale according to the DSM-IV), DISC-IV (The Diagnostic Interview Schedule for Children, Version IV), DSM-IV (The Diagnostic and Statistical Manual of Mental Disorders, 4th Edition), ICD-10 (International Classification of Diseases, 10th Edition), KMGQ (The Kinney Medical and Gynecological Questionnaire), MRSPFED (Modified schedule for risk and protective factors in early development), PSS (The Perceived Stress Scale) SADS-PL (Schedule for Affective Disorders and Schizophrenia – Present and Lifetime Version)

1.5 Research questions and hypotheses

The aim of the current study is to investigate the association between prenatal maternal stress and ADHD symptoms in the children. The effects of the timing of prenatal stress exposure will be examined in an explorative manner with no particular hypothesis. The potential association will also be investigated in light of postnatal maternal stress at the time of the evaluation of child symptoms and of postnatal paternal stress during infancy. Moreover, the possible moderating role of the child's sex will be examined. The research questions and hypotheses are presented below.

Question 1:	Is prenatal maternal stress associated with ADHD symptoms in the offspring?
Hypothesis 1:	Prenatal maternal stress is positively associated with ADHD symptoms in the offspring.
Question 2:	Are the effects of prenatal stress timing-specific?
Hypothesis 2:	No particular hypothesis is set, as previous research is inconclusive.
Question 3:	Are the effects of prenatal stress independent of postnatal levels of maternal and paternal stress?
Hypothesis 3:	The effects of prenatal stress are independent of postnatal parental stress, but also partially mediated by postnatal levels of maternal stress. The influence of postnatal paternal stress on the associations between prenatal maternal stress and child ADHD symptoms has not been previously examined, thus no hypothesis is set.
Question 4:	Are the associations between prenatal maternal stress and child ADHD symptoms different in boys and girls?
Hypothesis 4:	No particular hypothesis is set, as previous research is inconclusive.

2 Methods

2.1 Sample and subjects

This study is part of the multidisciplinary PREDO (Prediction and Prevention of Pre-eclampsia) project (Villa et al., 2013) that aims at investigating the prediction and prevention of pre-eclampsia and fetal growth restrictions as well as examining the effects of prenatal maternal stress on the developing fetus. The PREDO project involves three arms – obstetric, genetic and psychological – and the data has been collected longitudinally in two parts. The first sample was gathered between September 2005 and December 2009 and includes 973 pregnant women with risk factors for pre-eclampsia and 110 pregnant women without known risk factors for comparison. The second, epidemiological subsample consists of 3,702 pregnant women who were recruited between April 2007 and February 2010. All women were enrolled during their first ultrasound screening at 12 + 0 to 13 + 6 weeks of gestation in one of nine hospital maternity clinics (Women's Hospital, Kätilöopisto Maternity Hospital and Jorvi Hospital at Helsinki University Central Hospital, Kanta-Häme Central Hospital, Päijät-Häme Central Hospital, Tampere University Hospital, Kuopio University Hospital, Northern Karelia Central Hospital and Iisalmi Hospital). The recruitment process including the exclusion criteria has been described in more detail elsewhere (Villa et al., 2013). The PREDO study protocol has been approved by the Helsinki and Uusimaa Hospital District.

A total of 4,785 pregnant women expecting singletons were recruited and gave their written informed consent. The women were asked to fill out a background information form once in the beginning of the participation and a pregnancy diary every two weeks a total of 14 times during weeks 12 + 0 to 39 + 6 of pregnancy. The pregnancy diary consists of a number of questionnaires, including the Perceived Stress Scale (PSS; Cohen, Kamarck, & Mermelstein, 1983) which was filled out at each measuring point. The diary was completed by 3,415 women. The participants were followed up postpartum, and paternal PSS scores were collected at child age of six months (n = 1,608) and maternal PSS scores at child age of one to five years (n = 2,599). At the latter follow-up, the mothers were also asked to fill out the Conners' 10-item scale as a measure of child ADHD symptoms (n = 2,609).

For the present study, a total of 2,304 compliant subjects were included, which constituted 48.15 % of all women who originally consented to participate. Participants with missing values in the main variables used in the current study (prenatal stress during pregnancy

overall and child ADHD symptoms) were excluded (n = 2,481); in analyses with partially missing data the number of participants included is explicitly noted. To examine possible differences between subjects included and excluded from the current study, *t*- and chi-square tests were run.

Compared to participants with complete data on the main variables, women excluded from the present study were, on average, younger (mean (M) = 31.17 vs. M = 31.86 years, p < .001), less educated (52.13 % vs. 62.71 % had received tertiary education, p < .001), had a higher pre-pregnancy BMI (M = 24.83 vs. M = 24.29, p < .001), were more likely to have smoked at any point during pregnancy (10.63 % vs. 5.90 %, p < .001), to live without a partner (3.41 % vs. 1.59 %, p < .001), to be multiparous (64.40 % vs. 58.00 %, p < .001) and to give birth to a boy (53.81 % vs. 50.56 %, p = .03). However, the groups did not differ with regard to the length of gestation, child birthweight, alcohol consumption, hypertensive disorders or history of mental disorders (ps ≥ .07). In the excluded group, Conners' scores on child ADHD symptoms were available for 305 participants. These did not differ significantly from the scores of participants included in the study (p = .06). PSS scores on maternal stress experiences were available for 1,040 excluded women in the first trimester, 1,092 in the second trimester, 1,029 in the third trimester and 1,103 overall during pregnancy. Of these, women excluded from the current study had significantly higher levels of stress during the second trimester (M = 5.41 vs. M = 5.18, p = .02) and overall (M = 5.43 vs. M = 5.19, p = .01), but not during the first (p = .051) or third trimester (p = .07), as compared to the women included in the study.

2.2 Assessment methods

2.2.1 Parental assessment

Maternal experiences of stress during pregnancy and postnatal levels of maternal and paternal stress were measured with an abbreviated, five-item version of the Perceived Stress Scale (PSS; Cohen et al., 1983). The full-length PSS is a 14-item questionnaire designed to measure subjective experiences of stress during the last month. Shortened, ten- and four-item versions were also put forward by Cohen (1983), consisting of the questions most highly correlated with the 14-item scale. The questions included in the present study concern feelings and thoughts during the last two weeks, such as "How often have you felt that you

were unable to control the important things in your life?" and "How often have you felt that things were going your way?" (reversed question). The items are rated on a five-point scale (0 = never, 1 = almost never, 2 = sometimes, 3 = fairly often, 4 = very often), and a sum total ranging from 0 to 20 is calculated. Higher scores reflect higher levels of stress. The PSS has shown good reliability and validity in previous studies with both the 4- and 14-item versions (Cohen et al., 1983; Karam et al., 2012; Monroe, 2008; Nast, Bolten, Meinlschmidt, & Hellhammer, 2013). In the present study, the reliability of the scale improved by adding a fifth item from the full-length questionnaire ("How often have you felt nervous and 'stressed'?") resulting in good measures of internal consistency, with Cronbach's alphas at different measurement times ranging from .74 to .78.

In the current study, mean variables were computed for each pregnancy trimester separately and for the pregnancy overall using the sum totals of each measurement point. For each specific measurement point, missing values on three or more questions resulted in a "missing value" for that week. With missing values of two or less, the missing scores were replaced with the mean value calculated from the participant's scores obtained for that week. The mean variable for the pregnancy overall was computed using the mean variables of each trimester. However, the first trimester only included one measurement, which thus constituted all values available up to pregnancy week 13 + 6.

2.2.2 Child assessment

Child ADHD symptoms were evaluated using the Conners' 10-item scale. The questionnaire consists of ten statements derived from the Hyperactivity Index (HI) of the more comprehensive Conners' rating scales (Gianarris, Golden, & Greene, 2001) and is also known as the Conners Abbreviated Symptom Questionnaire (ASQ) and the Abbreviated Conners' Rating Scales for Parents (CPRS-HI; Westerlund, Ek, Holmberg, Näswall, & Fernell, 2009). The Conners' rating scales were developed to assess problematic behavior in children with a specific focus on hyperactivity (Gianarris et al., 2001). The Conners' 10-item scale is a concise measure of ADHD-like symptoms that has been shown to strongly discriminate between children with and without ADHD (Conners, 1999; Westerlund et al., 2009). Items are rated on a four-point scale (0 = never, seldom; 1 = occasionally; 2 = often, quite a bit; 3 = very often, very frequent) and measure hyperactive-impulsive behavior (e.g.

"Restless or overactive", "Inattentive, easily distracted") and emotional lability (e.g. "Cries often and easily", "Mood changes quickly and drastically") over the past month. Higher scores reflect a greater amount of ADHD symptoms. In line with previous studies (Conners, Sitarenios, Parker, & Epstein, 1998; Westerlund et al., 2009), the current study yielded a good internal reliability of .87 for the scale.

2.3 Background variables

The background variables were selected on basis of prior research linking the variables to maternal experiences of stress and/or child ADHD symptoms (Banerjee et al., 2007; Cohen & Janicki-Deverts, 2012; Linnet et al., 2003; Marin et al., 2014; Rodriguez et al., 2007; Woods et al., 2010).

Child sex. Information on the child's sex (0 = girl, 1 = boy) was obtained from the birth register.

Child age. The age of the children varied at follow-up. The age was measured in months.

Birthweight. Information on the child's birthweight was obtained from patient case reports for the high risk subsample and from the birth register for the epidemiological subsample. The birthweight was measured in grams and adjusted for length of gestation for the analyses.

Length of gestation. Information on the length of gestation was obtained primarily from the birth register, where it was measured in days, by subtracting the date of the mother's last menstrual period from the birth date of the child. In the case of missing information in the birth register, gestational duration was obtained from patient case reports or lastly from the pregnancy diaries. For this study, the length of gestation was transformed into weeks.

Maternal age. Maternal age at the time of childbirth was obtained from patient case reports for the high risk subsample and from the birth register for the epidemiological subsample. The age was measured in years.

Education. The mothers were asked to report their highest level of education on the background questionnaire on a 9-point scale: 1 = elementary school, 2 = middle school, 3 = primary school, 4 = high school, 5 = vocational school or equivalent, 6 = institute or equivalent, 7 = university of applied sciences, 8 = university, 9 = none of these. The levels

of education were grouped into two categories, where 1 = primary and secondary (elementary school, middle school, primary school, high school, vocational school or equivalent, institute or equivalent) and 2 = tertiary (university of applied sciences, university).

Family structure. Information on family structure (0 = mother living without partner, 1 = mother married or cohabiting) was obtained from the birth register.

History of mental disorders. The mothers were asked to report on the background questionnaire whether they had had any of the following mental disorders before pregnancy: depression, panic disorder, schizophrenia, other psychosis or other mental disorder. Of these, one variable was formed to reflect whether the mother did or did not have one or more of the abovementioned disorders (0 = no, 1 = yes).

Hypertensive disorders during pregnancy. Information on hypertensive disorders during pregnancy (0 = no hypertensive disorders, 1 = pre-eclampsia, gestational hypertension or chronic hypertension) was obtained from patient case reports for the high risk subsample and from the birth register for the epidemiological subsample.

Parity. Information on the number of previous children of the mother (0 = multiparous, 1 = primiparous) was obtained from the birth register.

Smoking. Information on mothers' smoking was obtained from the birth register and checked against the information on the background questionnaire (1 = did not smoke at all during pregnancy, 2 = quit smoking during the 1st trimester, 3 = smoked after the 1st trimester / throughout the pregnancy).

Alcohol consumption. The mothers were asked on the background questionnaire whether they consumed any alcohol during the pregnancy (0 = no, 1 = yes).

BMI. Maternal body mass index (kg/m^2) was calculated based on the height and weight of the mother prior to pregnancy, which were obtained from patient case reports for the high risk subsample and from the birth register for the epidemiological subsample.

2.4 Statistical methods

All analyses were performed using the Statistical Package of Social Science, version 22 (IBM SPSS 22 for Windows). Due to the PSS- and Conners' 10-item-scales' being right-skewed, the distributions were square root transformed for analyses to attain normality. All continuous variables were standardized (mean = 0, standard deviation = 1) to facilitate interpretation of effect sizes. Missing values in discrete variables were dummy-coded into their own category. Missing values in continuous covariates were imputed with the mean value of all respondents, with the exception of the key covariates "postnatal maternal stress" and "postnatal paternal stress", where no imputing was performed.

Correlations between continuous variables were assessed using Pearson's product-moment correlation coefficients. The associations between nominal background variables and prenatal stress and child ADHD symptoms were analyzed using *t* tests. Linear regression analyses were used in four different regression models to investigate whether maternal experiences of prenatal stress are associated with child ADHD symptoms in early childhood. The first regression model included child sex and age as covariates. In the second model, length of gestation and child birthweight adjusted for length of gestation, maternal age, education, family structure, history of mental disorders, hypertensive disorders during pregnancy, parity, smoking and alcohol consumption were also included. The third regression model accounted for postnatal maternal stress in addition. Finally, in the fourth model, paternal stress at child age of six months was also adjusted for.

Additional analyses were run to examine interaction effects between the sex of the child and prenatal stress on child ADHD symptoms, by entering the main effects of child sex and prenatal stress in the regression model together with their interaction terms. Interaction effects of prenatal and postnatal maternal stress on child ADHD symptoms were explored using the same method. Furthermore, after confirming the necessary criteria for mediation effects to have been met, mediation effects of postnatal maternal stress on the associations between prenatal stress and child ADHD symptoms were examined using the Sobel test.

3 Results

3.1 Sample characteristics

Sample descriptives are presented in Table 3. The final sample (n = 2,304) in the current study consisted of mothers in the age range of 18.01 to 47.39 years at childbirth (M = 31.86, standard deviation (SD) = 4.61) and of their children aged 1.92 to 5.92 years at follow-up (M = 3.48, SD = 0.71). Maternal stress scores decreased, on average, throughout pregnancy, but rose again postnatally and were highest at child age of one to five years. All differences in mean maternal stress scores between the trimesters and the follow-up were statistically significant (ps < .001). The correlations and mean differences regarding the main study variables and covariates are shown in Appendix 1. Higher levels of prenatal maternal stress were positively associated with smoking during pregnancy, shorter length of gestation, lower education, higher maternal BMI, being multiparous, having a history of mental disorders and living without a partner (ps < .05). Children with higher levels of ADHD symptoms were more likely to have had a lower birthweight, be a boy, have a lower age at follow-up, and be firstborn (ps < .05). Higher levels of child ADHD symptoms were also positively associated with a lower maternal age, maternal smoking during pregnancy and a maternal history of mental disorders (ps < .05).

3.2 Correlations between parental stress and child ADHD symptoms

The correlations between the main study variables are presented in Table 4. All measures of maternal stress, paternal stress and child ADHD symptoms were significantly intercorrelated. Child ADHD symptoms were most strongly correlated with postnatal maternal stress and least correlated with paternal stress at child age of six months. Prenatal maternal stress measures were highly significantly correlated with each other as well as with postnatal maternal stress. All measures of prenatal and postnatal maternal stress were also significantly and positively correlated with child ADHD symptoms.

Table 3. Sample descriptives.

Continuous variables	***N***	**Mean**	***SD***	**Range**
PSS				
Overall	2,304	5.19	2.50	0.10 - 18.50
1st trimester	2,207	5.52	3.33	0.00 - 19.00
2nd trimester	2,297	5.18	2.54	0.00 - 18.00
3rd trimester	2,235	4.85	2.75	0.00 - 17.50
6 months (father)	1,247	5.32	2.94	0.00 - 18.00
1–5 years	2,292	6.05	3.37	0.00 - 20.00
Conners' 10-item scale	2,304	5.98	4.53	0.00 - 28.00
Child age at follow-up (years)	2,304	3.48	0.71	1.92 - 5.92
Birthweight (g)	2,297	3,522.39	510.00	580.00 - 5,110.00
Length of gestation (weeks)	2,304	39.90	1.56	27.71 - 42.71
Maternal age (years)	2,304	31.86	4.61	18.01 - 47.39
Maternal BMI (kg/m^2)	2,261	24.29	4.87	15.92 - 52.34

Nominal variables	***N***	**%**
Child sex	*2,304*	
Boy	1,139	49.44
Girl	1,165	50.56
Education level	*2,293*	
Primary & Secondary	855	37.29
Tertiary	1,438	62.71
Smoking	*2,237*	
Did not smoke at all	2,105	94.10
Quit during the 1st trimester	69	3.08
Smoked after the 1st trimester	63	2.82
Alcohol	*1,958*	
No	1,669	85.24
Yes	289	14.76
History of mental disorder	*2,183*	
No	1,895	86.81
Yes	288	13.19
Hypertensive disorder	*2,283*	
No	2,020	88.48
Yes	263	11.52
Family structure	*2,201*	
Married or cohabiting	2,166	98.41
Living without partner	35	1.59
Parity	*2,299*	
Primiparous	965	41.97
Multiparous	1,334	58.03

Table 4. Correlations between the main study variables.

	1	2	3	4	5	6	7
1 PSS pregnancy overall	---						
2 PSS 1st trimester	.84***	---					
3 PSS 2nd trimester	.90***	.62***	---				
4 PSS 3rd trimester	.86***	.52***	.76***	---			
5 PSS father 6 months	.12***	.09**	.12***	.11***	---		
6 PSS 1–5 years	.46***	.36***	.43***	.43***	.14***	---	
7 Conners'	.19***	.14***	.19***	.17**	.06*	.21***	---

* $p < .05$, ** $p < .01$, *** $p < .001$

3.3 Associations between prenatal maternal stress and child ADHD symptoms

The results of the linear regression analyses are presented in Table 5. After adjusting for child sex and age, a significant association between maternal stress during pregnancy overall and child ADHD symptoms was found. For each one *SD* unit increase in prenatal stress, child ADHD symptoms increased by 0.19 *SD* units (Model 1). The addition of gestational age, birthweight adjusted for gestational age, maternal age at childbirth, education level, smoking, alcohol consumption, parity, pre-pregnancy BMI, family structure, hypertensive disorders during pregnancy and history of mental disorders to factors controlled for in Model 2 yielded an similar association reflecting 0.19 *SD* units higher child ADHD scores per each one *SD* unit higher prenatal stress.

Adjusting for postnatal maternal stress, measured at the time of child ADHD symptom assessment, was included in Model 3. Prenatal maternal stress remained a significant independent predictor of child ADHD symptoms, but the effect was nearly halved when postnatal maternal stress was accounted for, indicating a 0.12 *SD* unit increase in child ADHD scores per each one *SD* unit increase in prenatal stress. Adjusting for paternal stress in child's infancy (Model 4) had no impact on the effect size of prenatal maternal stress, but the certainty of the estimate was slightly reduced. Nonetheless, the association between prenatal maternal stress and child ADHD symptoms remained highly significant.

Table 5. Regression models for prenatal stress and ADHD symptoms in 1-5-year-old children.

	Pregnancy overall				**1st trimester**				**2nd trimester**				**3rd trimester**			
	n	***B***	**95 % CI**	***p***	***n***	***B***	**95 % CI**	***p***	***n***	***B***	**95 % CI**	***p***	***n***	***B***	**95 % CI**	***p***
Model 1	2,304	0.19	0.15 - 0.23	< .001	2,207	0.14	0.10 - 0.18	< .001	2,297	0.19	0.15 - 0.23	< .001	2,235	0.17	0.13 - 0.21	< .001
Model 2	2,304	0.19	0.15 - 0.23	< .001	2,207	0.14	0.10 - 0.18	< .001	2,297	0.19	0.15 - 0.23	< .001	2,235	0.18	0.14 - 0.22	< .001
Model 3	2,304	0.12	0.07 - 0.16	< .001	2,207	0.07	0.03 - 0.11	.001	2,297	0.12	0.07 - 0.16	< .001	2,235	0.11	0.07 - 0.15	< .001
Model 4	1,247	0.12	0.06 - 0.18	< .001	1,201	0.07	0.01 - 0.13	.020	1,247	0.12	0.06 - 0.18	< .001	1,230	0.11	0.05 - 0.17	< .001

B = unstandardized regression coefficient reflecting the change in child ADHD symptoms in standard deviation units per each standard deviation unit increase in prenatal maternal stress

95 % CI = 95 % confidence interval

Model 1: Adjusted for child sex and age.

Model 2: Adjusted also for gestational age, birthweight adjusted for gestational age, maternal age at childbirth, education level, smoking, alcohol consumption, parity, pre-pregnancy BMI, family structure, hypertensive disorders during pregnancy and history of mental disorders.

Model 3: Adjusted also for postnatal maternal stress.

Model 4: Adjusted also for paternal stress at child age of six months.

3.4 The timing of prenatal maternal stress and child ADHD symptoms

The same regression models analyzed for maternal stress during pregnancy overall were run for each pregnancy trimester separately (Table 5). The results are presented graphically in Figure 1. The associations between prenatal maternal stress in the 1st trimester and child ADHD symptoms were slightly weaker compared to the subsequent trimesters. For each one *SD* unit increase in 1st trimester prenatal stress, child ADHD symptoms increased by 0.14 *SD* units (Models 1 and 2). The association remained significant after controlling for postnatal maternal stress in Model 3, but the effect size was halved. The addition of paternal stress as a covariate in Model 4 resulted in the same 0.07 *SD* unit increase in child ADHD symptoms per each one *SD* unit increase in prenatal stress as in Model 3, however, with a slightly lower level of significance.

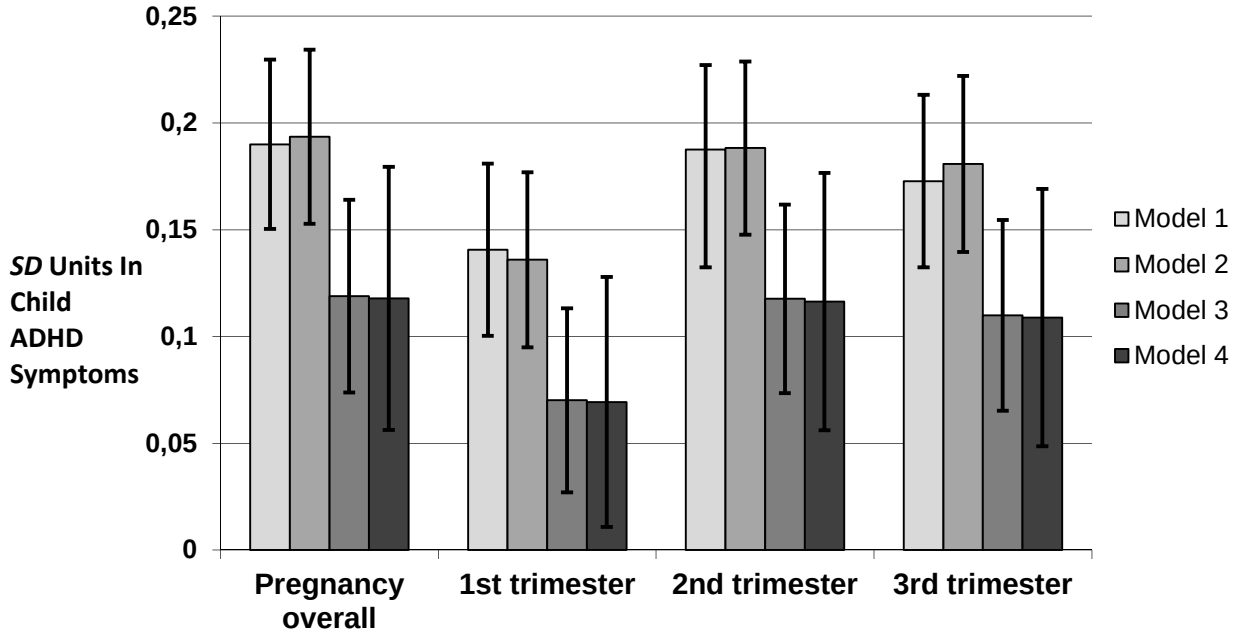

Figure 1. Associations between prenatal stress and child ADHD symptoms. Error bars illustrate the increase in ADHD scores with the 95 % CI in *SD* units per one *SD* unit increase in prenatal stress.

Model 1: Adjusted for child sex and age.

Model 2: Adjusted also for gestational age, birthweight adjusted for gestational age, maternal age at childbirth, education level, smoking, alcohol consumption, parity, pre-pregnancy BMI, family structure, hypertensive disorders during pregnancy and history of mental disorders.

Model 3: Adjusted also for postnatal maternal stress.

Model 4: Adjusted also for paternal stress at child age of six months.

The strongest associations between stress in a specific pregnancy trimester and child ADHD symptoms were found for the 2nd trimester. After adjusting for background variables, significant associations reflecting a 0.19 *SD* unit increase in child ADHD symptoms per each one *SD* unit increase in 2nd trimester stress scores were found (Models 1 and 2). For maternal stress in the 3rd trimester, the associations were only marginally weaker, with the respective *SD* unit increase values of 0.17 (Model 1) and 0.18 (Model 2). In both mid- and late-pregnancy, the addition of postnatal maternal stress (Model 3) and paternal stress (Model 4) as covariates resulted in lower, yet highly significant, effect sizes of 0.12 (2nd trimester) and 0.11 (3rd trimester).

3.5 Mediation effects of postnatal maternal stress on the associations between prenatal maternal stress and child ADHD symptoms

As seen in Table 4, prenatal maternal stress was significantly associated with both postnatal maternal stress and child ADHD symptoms, and postnatal maternal stress was also associated with child ADHD symptoms. In addition, as seen in Table 5, the effects of prenatal stress on ADHD symptoms in the offspring attenuated considerably in size after adjusting for postnatal levels of maternal stress. Therefore, mediation effects of postnatal maternal stress on the associations between prenatal maternal stress and child ADHD symptoms were explored. Since the controlling for other covariates did not have substantial effects on the associations, no covariates were included in the mediation analyses.

Results of the Sobel test suggested that the association between prenatal maternal stress during pregnancy overall and child ADHD symptoms was significantly mediated by postnatal maternal stress ($B_{indirect}$ = 0.10; z = 6.73, p < .001). When examining the associations regarding each pregnancy trimester separately, similar effects were found: postnatal maternal stress was a significant mediator of the influence of 1st trimester ($B_{indirect}$ = 0.07; z = 7.54, p < .001), 2nd trimester ($B_{indirect}$ = 0.07; z = 6.89, p < .001) and 3rd trimester ($B_{indirect}$ = 0.07; z = 7 .15, p < .001) prenatal stress on offspring ADHD symptoms. However, all mediation effects were partial, since prenatal maternal stress also exerted significant independent effects on child ADHD symptoms in the third and fourth regression models, as mentioned above.

3.6 Interaction effects of prenatal stress and child sex and of prenatal and postnatal maternal stress on child ADHD symptoms

Further analyses revealed a significant interaction between child sex and 1st trimester stress after adjusting for child age (p = .008). The results of the linear regression analyses run separately for boys and girls are presented in Table 6. Of children exposed to prenatal stress in the 1st trimester, boys had significantly higher levels of ADHD symptoms than girls in all four models (ps < .001). The effects of 1st trimester prenatal stress on child ADHD symptoms remained significant for boys across all four regression models. However, for girls, the addition of postnatal parental stress to factors controlled for (Models 3 and 4) rendered the associations between prenatal stress in the first trimester and child ADHD symptoms non-significant. No moderating effects of child sex were found for stress during the other trimesters nor for stress during pregnancy overall (ps ≥ .07). Nor did any interaction effects reach significance when examining the interaction between postnatal maternal stress and prenatal stress at any point during pregnancy (ps ≥ .16).

Table 6. Regression models for prenatal stress in the 1st trimester and child ADHD symptoms by sex.

	Boys				**Girls**			
	n	***B***	**95 % CI**	***p***	***n***	***B***	**95 % CI**	***p***
Model 1	1,120	0.20	0.14-0.25	< .001	1,087	0.09	0.03-0.14	.003
Model 2	1,120	0.19	0.13-0.25	< .001	1,087	0.09	0.03-0.15	.003
Model 3	1,120	0.12	0.06-0.18	< .001	1,087	0.03	-0.03-0.09	.40
Model 4	612	0.12	0.03-0.21	.007	635	0.02	-0.06-0.10	.60

B = unstandardized regression coefficient reflecting the change in child ADHD symptoms in standard deviation units per each standard deviation unit increase in maternal stress; 95 % CI = 95 % confidence interval

Model 1: Adjusted for child age.

Model 2: Adjusted also for gestational age, birthweight adjusted for gestational age, maternal age at childbirth, education level, smoking, alcohol consumption, parity, pre-pregnancy BMI, family structure, hypertensive disorders during pregnancy and history of mental disorders.

Model 3: Adjusted also for postnatal maternal stress.

Model 4: Adjusted also for paternal stress at child age of six months.

4 Discussion

The focus of this study was on investigating the association between prenatal maternal stress and child ADHD symptoms in early childhood in the offspring. The main objectives were to examine whether prenatal stress exposure is associated with higher levels of child ADHD symptoms, and whether the strength of the association differs according to the timing of the stress exposure. This study is unique in that the associations were investigated controlling for a wide array of covariates, specifically including postnatal measures of both maternal and paternal levels of stress, which have not been included in previous studies. Moreover, for the first time, to my knowledge, the possible mediation effects of postnatal maternal stress on the associations between prenatal stress and child ADHD symptoms were explored. Finally, the moderating effects of child sex and of postnatal maternal stress on the associations between prenatal stress and child ADHD risk were examined.

Prenatal maternal stress was significantly associated with higher levels of ADHD symptoms in the offspring. The associations were significant for stress during pregnancy overall and for each pregnancy trimester separately. Higher levels of prenatal stress were independently associated with higher levels of child ADHD symptoms after controlling for a comprehensive list of covariates – after including measures of postnatal maternal and paternal stress, for each one standard deviation unit increase in prenatal stress, child ADHD symptoms increased by 0.12 *SD* units. Mid- to late-pregnancy stress had the strongest associations with child ADHD symptoms, while early-pregnancy stress showed a slightly weaker, yet significant, effect. For each one *SD* unit increase in 1st trimester prenatal stress, child ADHD symptoms increased by 0.07 *SD* units. The effect sizes regarding 2nd and 3rd trimester stress were 0.12 and 0.11, respectively.

The associations between prenatal maternal stress and child ADHD symptoms were partially mediated by postnatal maternal stress. Nevertheless, after controlling for postnatal maternal stress, the independent effects of prenatal stress remained highly significant for all exposure windows excluding the first trimester, where the significance was slightly reduced but still statistically significant. Adjusting for postnatal paternal stress had no impact on the effect sizes, but the certainty of the estimates was slightly reduced, most likely due to reductions in sample size and, therefore, statistical power in these analyses. Nonetheless, the levels of significance of the associations between prenatal maternal stress and child ADHD symptoms remained the same as after controlling for postnatal maternal stress: significant for first

trimester stress and highly significant for all other exposure time points. Additionally, the sex of the child was found to moderate the association between prenatal stress and child ADHD symptoms, but only regarding early-pregnancy stress. Among boys, prenatal stress during the first trimester independently predicted higher levels of ADHD symptoms, whereas, among girls, no significant associations were found for early-pregnancy stress after postnatal maternal stress was accounted for. No interaction effects regarding child sex were found for the other trimesters nor for pregnancy overall. No significant interaction effects of prenatal and postnatal maternal stress were found, either.

4.1 Associations between prenatal maternal stress and child ADHD symptoms

Exposure to prenatal maternal stress during pregnancy overall was significantly associated with child ADHD symptoms in early childhood. Higher levels of prenatal stress were associated with higher levels of child ADHD symptoms after controlling for a comprehensive list of covariates, including measures of postnatal parental stress. The results are in line with my hypothesis and consistent with the findings of the majority of previous studies (Class et al., 2014; Grizenko et al., 2008; Grizenko et al., 2012; Kim et al., 2009; Li et al., 2010; Martini et al., 2010; Motlagh et al., 2010; Park et al., 2014; Rodriguez & Bohlin, 2005; Ronald et al., 2011). The effect sizes found in the current study are also proportional to previous findings, considering the differences in covariates included, specifically postnatal maternal stress (Rodriguez & Bohlin, 2005).

In addition to the uniqueness of including postnatal maternal and paternal stress as covariates, the current study is, to my knowledge, the first to employ the combination of a large, representative sample with reliable, prospective and frequent assessments of prenatal stress in examining the associations between prenatal maternal stress and child ADHD symptoms. Most previous studies have used restricted measures of prenatal stress, either due to the confining to a certain category of stress (Class et al., 2014; Grizenko et al., 2008; Grizenko et al., 2012; Li et al., 2010) or to a highly simplified measure of stress (Class et al., 2014; Li et al., 2010; Martini et al., 2010; Park et al., 2014). In two very large (*n*s > 700,000), population-based studies prenatal maternal stress was found to be a significant predictor of subsequent ADHD symptoms in the offspring (Class et al., 2014; Li et al., 2010), despite the

definition of stress being constricted to solely narrowly defined stress caused by bereavement. In another relatively large (n = 992), community cohort sample, prenatal maternal stress, as assessed by only one question, was also significantly associated with ADHD ever diagnosed in 14–27-year-old offspring, after adjusting for maternal depressive disorders after birth (Martini et al., 2010). While, parallel to the present study, Rodriguez and Bohlin (2005) focused on general maternal stress using a reliable scale for measurement and found that *in utero* exposure to general maternal stress independently contributed to offspring ADHD symptoms in 7-year-old children, their sample size was substantially smaller (n = 208) than the current sample, and no postnatal measures of maternal stress were controlled for.

Evidence of prenatal maternal stress predicting ADHD behaviors in the offspring has previously been found mainly in school-aged children. Apart from the bereavement stress - studies by Class and colleagues (2014) and Li and colleagues (2010), only one study focused on ADHD symptoms in toddlers. Corresponding to my findings, maternal stressful events during pregnancy were significantly associated with ADHD symptoms in 2-year-old children both among boys and girls, after adjusting for covariates, including postnatal maternal wellbeing (Ronald et al., 2011). However, the postnatal covariate was measured shortly after having given birth, and only reflected postpartum mood. Parallel to the present study, Ronald and colleagues (2011) used a large community sample. The findings from the current study expand the results concerning toddlers and preschoolers, showing significant associations between prenatal stress exposure and higher levels of ADHD symptoms in early childhood, in children aged one to five. This is an important finding, as early intervention has been found the most effective in preventing ADHD (Jones, Daley, Hutchings, Bywater, & Eames, 2007; McGoey, Eckert, & Dupaul, 2002).

In contrast with several previous studies, showing limited generalizability due to sample composition, the current study employed a large, representative community sample. Significant associations between prenatal maternal stress and ADHD symptoms in the children have been found in four clinical samples, which have all, in addition, been small in size (Grizenko et al., 2008; Grizenko et al., 2012; Motlagh et al., 2010; Park et al., 2014). Furthermore, the assessments of maternal stress in these studies have been substantially coarser than the method of evaluation used in the current one, and based solely on retrospective reports. Despite prenatal maternal stress exposure having been associated with

child ADHD in the abovementioned samples, the findings have limited external validity and may not be directly applicable to the normal population, since clinic-referred children may not be representative of all children exhibiting ADHD symptoms. However, the current study extends previous findings by showing similar associations in a representative community sample. Although case-control studies are suited for cases where the outcome of interest is rare, this is not the case for children exhibiting ADHD *symptoms* – that have, equally to diagnosable ADHD, been associated with prenatal maternal stress (Kim et al., 2009; Park et al., 2014) – especially in large samples, such as the one used in the present study.

Nevertheless, although in line with most previous studies, the current study findings are not directly in agreement with the conclusions drawn by Rice and colleagues (2010), who found no significant associations between prenatal stress and offspring ADHD symptoms in unrelated mother-child pairs. However, compared to the current study, they used a substantially smaller (unrelated n = 205) and less representative sample consisting of participants recruited from fertility clinics. The average maternal age was unusually high (unrelated M = 38.92 vs. current study M = 31.86), which may play an explanatory role in the contradictory findings, since low maternal age has been associated with an increased risk of child ADHD (Valdimarsdottir et al., 2006). In addition, the developmental differences present in 4-10 -year-olds are considerable, which may have further blurred the potential genotype-independent effects of prenatal maternal stress on child ADHD symptoms.

Rice and colleagues (2010) were, thus far, the only ones to compare genetically related and unrelated mother-child pairs. Despite the lack of significant associations in the unrelated dyads, they found a significant association between prenatal stress and offspring ADHD in the related pairs. As all other studies on the topic, including the current one, have been conducted with genetically related dyads, the results are, in fact, not contradictory. In effect, the findings may shed light on the mechanisms responsible for the transmission of effects from mother to child: As the influence of environmental stimuli on genetically programmed development is thought to be epigenetically mediated (Bock et al., 2014), the effects of prenatal stress may not occur to the same extent in the absence of shared genes. Also, although interesting, the clinical relevance of child ADHD risk not being linked to prenatal stress in non-related dyads is relatively small, since the vast majority of children are born to their biological mothers.

Prenatal maternal stress has now been repeatedly associated with an increased risk of offspring ADHD (Class et al., 2014; Grizenko et al., 2008; Grizenko et al., 2012; Kim et al., 2009; Li et al., 2010; Martini et al., 2010; Motlagh et al., 2010; Park et al., 2014; Rodriguez & Bohlin, 2005; Ronald et al., 2011). The current study importantly adds to previous findings by showing the associations to hold for general, subjectively and frequently assessed maternal stress during pregnancy. Although posing difficulties for straightforward comparison, the use of widely varying stress measurement methods in different studies indicates that exposure to prenatal stress regardless of its type does increase the likelihood of ADHD symptoms in the offspring. As the current results corroborate by showing associations with general ADHD symptoms, as opposed to full syndrome diagnosable ADHD, the impact of prenatal stress may already be detected in children with sub-threshold ADHD (Kim et al., 2009), suggesting the link between prenatal stress and child attention hyperactivity problems to be robust despite the moderate effect sizes.

4.2 The timing of prenatal maternal stress and child ADHD symptoms

The effects of prenatal maternal stress on child ADHD symptoms differed based on the timing of the stress exposure. Stress experienced during the 2nd and 3rd trimesters was most strongly associated with higher levels of child ADHD symptoms, while prenatal stress in the first trimester had a smaller effect on child ADHD symptoms compared to the subsequent trimesters.

The results from the current study showing mid- to late-pregnancy stress to have the strongest associations with child ADHD symptoms are in line with most previous findings (Class et al., 2014; Grizenko et al., 2008; Li et al., 2010). Parallel to the present study, Grizenko, Shayan and colleagues (2008) found maternal stress at any point during pregnancy to significantly predict higher ADHD risk in the offspring, with late-pregnancy stress showing the strongest associations. However, Grizenko, Shayan and colleagues' study was based on a small (n = 203), clinical sample comprised mainly of boys (n = 171) with no control group, thus showing limited generalizability to the normal population and to girls. The large (ns > 700,000), registry-based studies by Class and colleagues (2014) and Li and colleagues (2010) also showed late-pregnancy stress to be most strongly associated with child ADHD. However, they only assessed bereavement stress caused by the death of a close

relative, which is likely to capture a mere fraction of women experiencing stress during pregnancy: Of all children included in Class and colleagues' study, 0.90 % were identified as having been exposed to prenatal stress, while experiencing stress during pregnancy is known to be common with prevalence estimates of 26-84 % (Rondo et al., 2003; Woods et al., 2010). Hence, conclusions drawn from the aforementioned studies regarding the impacts of generic prenatal stress are severely limited.

The current findings are in conflict with the results presented by Rodriguez and Bohlin (2005). In their study, early-pregnancy stress was reported to account for the largest portion of variance in child ADHD symptoms. However, the findings may not be directly comparable. The researchers tested for timing effects by entering successive assessments in chronological order into hierarchical multiple regression analyses, while, in the current study, the different trimesters were analyzed separately to avoid multicollinearity. As the highly intercorrelated (r = .54-.81) stress variables were analyzed simultaneously by Rodriguez and Bohlin, the controlling for early-pregnancy stress may have reduced the actual contributions of mid- and late-pregnancy stress leading to flawed interpretations of the significance of later-pregnancy stress. Thus, the conflicting results may be partly due to differing methods of analysis, but further research on the significance of exposure timing is warranted.

As the effects of the timing of prenatal maternal stress on child ADHD symptoms have, so far, only been researched in a handful of studies, which all have lacked in generalizability due to sample composition (Grizenko et al., 2008), constricted definition of stress (Class et al., 2014; Li et al., 2010) or flawed statistical analyses (Rodriguez & Bohlin, 2005), the present findings provide valuable evidence supporting the predictive value of mid- to late-pregnancy stress. Furthermore, previous findings pointing to stronger effects for late-pregnancy stress have relied on registry-based and retrospective reports, which may be considered especially questionable when assessing stress severity differences over a period of months, six to twelve years later (Grizenko et al., 2008).

The stronger impact of mid- to late-pregnancy stress may reflect chronicity. Stress experienced in the latter part of pregnancy is likely to continue postnatally (Pesonen et al., 2005), and postnatal stress has been associated with an increased risk of child attention problems (Dawson et al., 2000). In addition to the probability of onward continuity, stress in the latter part of pregnancy is likely to have commenced earlier in pregnancy, as reflected

in the high intercorrelations between the prenatal stress assessments (r = .52-.76) in the current study. As the present study showed average maternal stress levels to significantly decrease throughout pregnancy, part of the early-pregnancy stress is likely to have been short-term, while stress evident in later-pregnancy is likely to have continued longer. The duration of the stress exposure is known to be of importance with respect to the degree of adverse effects on the offspring (Xu et al., 2013). Also, as mothers' sensitivity to stress has been shown to diminish towards the end of pregnancy (Kammerer et al., 2002), stress reported in late-pregnancy may have been, if measured objectively, higher than the same levels of self-reported stress earlier in pregnancy. This may further explain the stronger associations with child ADHD symptoms found for mid- to late-pregnancy stress.

4.3 Effects of child sex on the associations between prenatal maternal stress and child ADHD symptoms

A significant interaction between prenatal maternal stress and the sex of the child was found for the first pregnancy trimester. Boys exposed to 1st trimester stress showed significantly higher levels of ADHD symptoms than girls with 1st trimester stress, after adjusting for child age. The results are in line with previous findings showing stronger associations between prenatal stress and ADHD in boys as compared to girls (Li et al., 2010; Rodriguez & Bohlin, 2005). Despite the similarities to the current study – the use of a prospective design, a community sample and the PSS for measuring stress – Rodriguez and Bohlin (2005) did not find any significant associations among girls. However, the sample used by Rodriguez and Bohlin was small (n = 208) and the amount of participants eventually developing ADHD minuscule (n = 7, i.e. 3.4 %). Despite the large percentage of girls (50.7 %) participating in the study, all seven children fulfilling all ADHD criteria were boys, and of the children fulfilling partial criteria of ADHD (n = 87), a clear minority is likely to have been girls (the ratio was not reported), as the prevalence of ADHD is known to be significantly higher in boys (Smalley et al., 2007). In the current study, the associations between 1st trimester prenatal stress and child ADHD symptoms were much weaker for girls than for boys, and after accounting for postnatal maternal stress, the associations among girls were no longer statistically significant.

On the other hand, results from another Swedish population-based sample, substantially larger in size (n = 738,144), did not show any moderating effects of child sex (Class et al.,

2014). However, the study only included binary measures of both bereavement stress and child ADHD, did not control for postnatal stress exposure, and rendered significant associations with child ADHD only regarding 3rd pregnancy trimester stress. Most likely due to the highly constricted indicators of child ADHD and especially of prenatal stress, despite the large sample size, the number of participants exposed to prenatal bereavement stress *and* eventually developing ADHD was extremely small (*n* = 149, i.e. 0.02 %), with half less participants exposed to 1st (*n* = 34) than 3rd trimester (*n* = 70) stress. Li and colleagues (2010) also used a similar, large, Danish community sample (*n* = 1,015,912), and found significant associations only in boys. However, again, the number of children with ADHD whose mothers were bereaved of a close relative during pregnancy was very small with respect to the sample size (n = 300, i.e. 0.03 %; boys *n* = 250 and girls *n* = 50). The researchers noted that their data on girls was scarce and that no firm conclusions could be drawn regarding the moderating effects of child sex.

While, as mentioned above, ADHD is known to be far more common in boys than girls (Smalley et al., 2007), and prenatal stress has been found to affect cognitive aspects, such as attention, more in boys than in girls (O'Connor et al., 2002), environmental risk factors associated with ADHD have not been found to have significantly different effects based on the sex of the child (Silva et al., 2014). As no moderating effects of child sex were found in the current study for stress during the 2nd or 3rd trimesters, nor for stress during pregnancy overall, it remains unclear whether the sex difference found regarding 1st trimester stress is truly substantially different from later-pregnancy stress, or whether it rather reflects statistical bias resulting from the lower reliability of 1st trimester stress data (derived from only one measurement of prenatal stress) compared to the subsequent pregnancy trimesters.

4.4 Effects of postnatal parental stress on the associations between prenatal maternal stress and child ADHD symptoms

The current study is, thus far, to the best of my knowledge, the first to consider the effects of postnatal maternal and paternal stress on the associations between prenatal maternal stress and child ADHD risk. After adjusting for postnatal maternal stress, measured concurrently with child ADHD symptoms, prenatal stress remained a significant independent predictor of child ADHD symptoms for all time periods of prenatal stress, but the effect sizes were nearly

halved. Further analyses showed that the associations between prenatal maternal stress and offspring ADHD symptoms were partially mediated by postnatal maternal stress. The results support my hypothesis and provide valuable new information on the mediation effects of postnatal maternal well-being on the associations between prenatal stress and child ADHD symptoms (O'Connor et al., 2003; Rice et al., 2010; Ronald et al., 2011).

Postnatal maternal well-being has been shown to influence child psychopathology (Assel et al., 2002; Dawson et al., 2000; O'Connor et al., 2003). Nevertheless, to my knowledge, no previous studies on prenatal stress and offspring ADHD have adequately controlled for postnatal factors at the time of child symptom assessment. Current maternal anxiety and depression have been found to significantly mediate the influence of prenatal maternal stress on child anxiety symptoms, both in genetically related and unrelated dyads (Rice et al., 2010). Similarly, adjusting for maternal or paternal symptoms of depression and anxiety at the time of child ADHD assessment has been found to substantially attenuate the associations between respective prenatal parental stress and child behavioral symptoms in 3-year-olds (Van Batenburg-Eddes et al., 2013). Yet, other findings have been contrary: Maternal anxiety at 8, 21 and 33 months postnatally has not been found to have any effect on the size of the association between prenatal maternal anxiety and behavioral/emotional problems in 4-year-old children (O'Connor et al., 2002). However, O'Connor and colleagues did not assess maternal well-being concurrently with the evaluation of child symptoms, thereby not, in fact, addressing the same exact question.

The findings from the current study offer new insights into the factors implicated in the associations between prenatal stress and child ADHD symptoms. Exposure to both prenatal and postnatal maternal stress did not result in statistically significant interaction effects, lending no support to moderating effects of postnatal stress on the associations between prenatal stress and child ADHD symptoms. However, postnatal maternal stress was found to be a significant mediator of the influence of prenatal stress on child ADHD symptoms – for stress during pregnancy overall and for each trimester separately. Together, these results suggest that exposure to prenatal maternal stress predicts increased risk of child ADHD, and that it does so partly by increasing levels of maternal stress during childhood. The results corroborate the importance of accounting for postnatal maternal well-being in investigations of child outcome, but further research is merited to disentangle the impacts of pre- and postnatal risk factors on child development.

The addition of paternal stress, measured at child age of six months, to covariates had no impact on the magnitude of prenatal stress prediction on child ADHD symptoms – only the certainty of the estimates was slightly reduced, most likely due to reductions in sample size. Postnatal paternal depression during the infant's early months has previously been associated with an increased risk of behavioral problems in 3–5-year-olds (Ramchandani et al., 2005), but, to my knowledge, no studies investigating the effects of paternal stress on child ADHD symptoms have been conducted. The current results suggest that paternal stress during infancy does not significantly affect the prediction of child ADHD risk by prenatal maternal stress. Moreover, the findings lend support to the hypothesis of direct intrauterine mechanisms as opposed to external environmental factors being central to the associations between prenatal stress and child outcomes, as externally mediated effects could be equally conveyed through paternal influences (Smith, 2008). However, including prenatal paternal stress measures as well as a paternal stress evaluation concurrently with child symptom assessment would be necessary to further investigate this assumption.

4.5 Underlying mechanisms

The mechanisms underlying the associations between prenatal maternal stress and ADHD symptoms in the offspring are still speculative and ostensibly extremely complex. The mediating factors are likely to operate on multiple epigenetic, physiological and psychological levels. However, due to practical restrictions, most studies aiming at uncovering the mechanisms driving the observed associations have only been able to focus on a limited number and sort of variables at once.

On a general level, several shared elements between women experiencing stress and children with ADHD symptoms have been discerned. A number of sociodemographic factors have been independently associated with child ADHD symptoms (Sagiv, Epstein, Bellinger, & Korrick, 2013), some of which have likewise been associated with higher levels of stress (Boyd, 2002; Woods et al., 2010). Adverse birth outcomes have been noted in association with both prenatal stress (Wadhwa, 2005; P. Zhu et al., 2010) and children with ADHD (Anderson et al., 2011; Heinonen et al., 2010). Moreover, smoking has been associated with experiencing stress (Ng & Jeffery, 2003) as well as with subsequent ADHD symptoms in the offspring of pregnant women (J. Zhu et al., 2014). However, the associations between

prenatal maternal stress and child ADHD symptoms may only be partially explained by these mutual features, as most studies, including the current one, have adequately controlled for these background variables, yet yielded significant associations. Furthermore, in the current study, adjusting for multiple sociodemographic and perinatal factors had virtually no effect on the magnitude of prenatal stress prediction of child ADHD symptoms, suggesting the primary linking mechanisms to lie elsewhere.

Research settings involving physiological and neuroanatomical aspects have contributed to the understanding of how prenatal stress is associated with the neurobehavioral development of the offspring. Exposure to prenatal maternal stress has been shown to shape brain development as witnessed in reductions in gray matter volumes, including the prefrontal cortical regions (Buss et al., 2010) that are vital to sustaining attention and controlling impulses (Asplund, Todd, Snyder, & Marois, 2010). Similar alterations in brain volumes have been found in children exhibiting ADHD symptoms (Aguiar et al., 2010; Valera et al., 2007). Maternal stress has been found to alter the neurochemical functioning of prenatally exposed offspring (Pallarés & Antonelli, 2014), and compelling evidence indicates parallel impairments in the dopaminergic and noradrenergic neurotransmitter systems in children with ADHD (Aguiar et al., 2010). However, studies investigating the abovementioned potential mechanisms specifically in relation to the effects of prenatal stress on offspring ADHD have not, to the best of my knowledge, yet been conducted.

A central mediator of maternal influences to the fetus is the placenta (Jansson & Powell, 2007). Maternal stress during pregnancy has been found to decrease the expression of the placental enzyme 11β-HSD-2 (O'Donnell et al., 2012), allowing higher levels of the stress hormone cortisol into the fetal compartment (Murphy et al., 2006). In animal studies, decreased 11β-HSD-2 activity and excessive fetal exposure to cortisol (Coe, Lubach, Crispen, Shirtcliff, & Schneider, 2010; Owen & Matthews, 2007; Schneider et al., 1999) have been associated with symptoms of inattention and hyperactivity in the offspring. However, evidence of similar mechanisms relating prenatal stress to ADHD symptoms in humans is less clear. Recurrent prenatal corticosteroid exposure has been associated with child attention problems (Crowther et al., 2007; French, Hagan, Evans, Mullan, & Newnham, 2004; Khalife et al., 2013), but confirming results regarding long-term neurodevelopmental outcomes in the children have yet to be established (Crowther, McKinlay, Middleton, & Harding, 2013). Other abnormalities in placental functioning have

also been implied as potential mediators of prenatal stress on child ADHD: prenatal psychosocial stress has been associated with compensatory placental growth (Tegethoff, Greene, Olsen, Meyer, & Meinlschmidt, 2010a), and increased placental size has been discovered in association with ADHD symptoms in 8- and 16-year-old offspring (Khalife et al., 2012). Increased placental growth – occurring as a compensatory mechanism to ensure sufficient fetal nutrient supply (Tegethoff et al., 2010a) – often results in a normal birthweight, despite the qualitative degradation of nutrient delivery to the fetus (Jansson & Powell, 2007). Thus, using birthweight as a proxy of placental functioning is not reliable, and, on the other hand, a lack of effect of birthweight on the associations between prenatal stress and child ADHD symptoms, like in the current study, does not preclude the possibility of placental mechanisms driving the effects of prenatal stress on offspring ADHD risk.

Other physiological pathways could include problems in child HPA-axis functioning. The development of the fetal HPA-axis is regulated by the limbic system, which is highly sensitive to exogenous glucocorticoids passing through the placenta (S. G. Matthews, 2000). Dysregulation of HPA-axis activity has been found in children exposed to prenatal stress (Glover et al., 2010), and similarly, in children exhibiting ADHD symptoms (Ma et al., 2011). The HPA-axis is known to be highly reactive in infancy and prone to alterations in association with deficient care and (maternal perceptions of) negative child temperament (Gunnar & Cheatham, 2003), which have, in turn, been associated with exposure to pre- and postnatal maternal stress (Assel et al., 2002; Pesonen et al., 2005). As the fetal HPA-axis becomes functional in mid-pregnancy (Gitau et al., 2001), it may be less vulnerable to stress-induced teratogenic effects earlier, which may partly account for the current findings showing higher levels of offspring symptoms to be associated with mid- to late-pregnancy stress.

The complexity of the mechanisms underlying the associations between prenatal maternal stress and child ADHD symptoms can be seen in findings linking maternal diet during pregnancy to child ADHD risk. Ingestion of high amounts of licorice during pregnancy has been associated with attention problems in 8-year-old offspring independently of covariates including prenatal stress (Räikkönen et al., 2009). The findings have been explained by evidence showing glycyrrhetinic acid, found in licorice, acting as an inhibitor of placental 11β-HSD-2 (Benediktsson, Calder, Edwards, & Seckl, 1997). As experiencing stress is known to increase unhealthy eating behaviors, such as the consumption of sweets (Hurley et

al., 2005), the pathways linking prenatal maternal stress to offspring neurobehavioral outcome could possibly involve such intricacies.

Investigations of gene-environment interactions have also shed light on the complexities involved in the associations between prenatal maternal stress and offspring ADHD symptoms. A specific genotype (DRD 7/7) has been suggested to interact with maternal stress during pregnancy resulting in more severe ADHD symptoms compared to children exhibiting a different genotype (Grizenko et al., 2012). Interestingly, no gene-environment interactions were detected in another study focusing on the same DRD 7/7 -genotype and prenatal nicotine exposure, despite their independent associations with child ADHD symptoms (Altink et al., 2008). The results could indicate that the interactions between environmental factors and offspring neurodevelopmental outcomes are extremely specific, and that each combination of ADHD predisposing genotypes and environmental insults may have distinct patterns of effect on the offspring. In the same vein, each genetic variant associated with ADHD has been found to explain only a minor percentage of heritability (Akutagava-Martins, Salatino-Oliveira, Kieling, Rohde, & Hutz, 2013).

The physiological mechanisms described above may be regulated through epigenetic processes. Environmental insults during the fetal period may induce alterations in gene expression, hence programming fetal development and leading to long-term changes in phenotype (Mill & Petronis, 2008; Monk et al., 2012). Evidence from animal studies has associated exposure to gestational stress with altered DNA methylation in the fetal brain (Mueller & Bale, 2008; Palacios-García et al., 2015). In humans, brain tissue is inaccessible in living subjects, but prenatal exposure to an objective measure of maternal stress has been associated with decreased DNA methylation in peripheral tissues in 13-year-old offspring (Cao-Lei et al., 2014). Correspondingly, lower levels of peripheral DNA methylation in several genes at birth have been associated with higher levels of child ADHD symptoms at six years of age (van Mil et al., 2014). Furthermore, the expression of enzymes responsible for DNA methylation maintenance has been found to be significantly lower in male than female placentas (Mueller & Bale, 2008), indicating physiological differences between the sexes in areas critical in neurodevelopment from early on, and possibly contributing to the tentative differences in prenatal stress prediction on the development of neurobehavioral disorders in males and females. Taken together, that the amount of genes proposed to contribute to the onset of ADHD is vast (Faraone, Bonvicini, & Scassellati, 2014), and excessive stress hormone exposure during pregnancy has been shown to alter the regulation

of over 1600 genes in the fetal brain (Salaria et al., 2006), the routes through which prenatal maternal stress may influence offspring neurodevelopment are myriad, and further research on the underlying mechanisms is warranted.

4.6 Implications of the findings

The present study indicates that exposure to prenatal maternal stress poses an increased risk of inattention and hyperactivity symptoms in toddlers and preschool-aged children. Maternal stress may have adverse effects on the neurobehavioral development of the offspring already in early-pregnancy, and increasingly so with stress exposure towards the end of pregnancy. Since ADHD is a common and persistent neurobehavioral disorder among children (Faraone et al., 2003; Wolraich et al., 2011) and may pervasively influence an individual's life (Hinshaw, 2002), and maternal experiences of stress are often long-lasting (Monk et al., 2012) – supported also by the moderate to strong correlations between maternal stress assessments in the present study – and the possible mediating mechanisms are numerous, focusing on measures aiming at minimizing stress during pregnancy in order to prevent detrimental influences on the offspring is imperative.

Some psychosocial interventions have shown promising results for reducing stress during pregnancy. Mind-body interventions, such as yoga (Beddoe, Paul Yang, Kennedy, Weiss, & Lee, 2009) and guided imagery (Rees, 1995), have been associated with decreased maternal stress and anxiety. Psychosocial services combined with group education have been found to significantly lower maternal stress levels during pregnancy (Affonso, De, Korenbrot, & Mayberry, 1999), and weekly telephone calls (Bullock, Wells, Duff, & Hornblow, 1995) and stress reduction instructions (Urizar et al., 2004) have proven effective in decreasing maternal experiences of stress. Despite the mixed results of intervention benefits in other studies (Urech et al., 2010; Vieten & Astin, 2008), no harmful effects of mind-body interventions have been reported, either (Marc et al., 2011).

Alongside implementing interventions for prenatal maternal stress, attention should also be paid to protective factors. Ensuring adequate rest, physical exercise, healthy eating habits and avoidance of alcohol and tobacco (E. D. Barker et al., 2013; Bhagat et al., 2015; Mei-Dan et al., 2014; Weissgerber et al., 2006) – all of which have been negatively associated with increased levels of stress (Hurley et al., 2005; Ng & Jeffery, 2003; Teegarden & Bale,

2008) – are important in promoting both maternal and fetal well-being during pregnancy. Also, social support during pregnancy has been found to buffer detrimental effects of maternal stress on fetal development by reducing the secretion of cortisol (Giesbrecht et al., 2013). As experiencing stress during pregnancy is common (Woods et al., 2010), and the vast majority of expecting mothers are reached frequently through maternity care visits, the influence of effective preventive actions may be widespread. Also, screening for maternal stress, as opposed to anxiety or depression, has been found to identify more women symptomatic during pregnancy – even of women with clinically diagnosable anxiety or depression (Vieten & Astin, 2008). This finding also corroborates focusing research on generic stress, rather than on more narrowly defined classes of psychiatric mood symptoms.

While preventive efforts may and should be focused already on the prenatal period, interventive actions in the postnatal period have also shown promise. Optimal postnatal care of the offspring has been shown to completely counteract the adverse effects of prenatal stress in rodents (Lemaire, Lamarque, Le Moal, Piazza, & Abrous, 2006), and researchers have speculated on the possibility of similar effects in humans (Grizenko et al., 2008), since the neonatal period is known as a time of robust neurogenesis (Sanai et al., 2011). Conversely, deficient postnatal care has been associated with poorer neurobiological outcomes in children (Gunnar & Cheatham, 2003) and is more likely to occur in the presence of high levels of maternal stress (Assel et al., 2002). As practically all known environmental risk factors for ADHD are known to occur in the fetal or neonatal period (Banerjee et al., 2007), focusing preventive efforts on the early developmental stages is essential. Furthermore, to target preventive actions most efficiently, future research should implement prospective designs with multi-level approaches in order to gain further insight into the mechanisms involved in the associations between prenatal maternal stress and offspring neurobehavioral outcomes.

4.7 Strengths and limitations of the study

The current study has several notable methodological strengths. The prospective design allowed the inspection of temporal sequence between exposure and outcome while minimizing recall-bias, and the large community-based sample provided a representative group of subjects from different backgrounds. The use of several sources for background

information (patient case reports, birth register and background questionnaires) provided information on a wide array of covariates. Furthermore, the present study is unique in that it considered the effects of postnatal paternal stress during infancy and of postnatal maternal stress concurrently with the evaluation of child ADHD symptoms on the associations between prenatal maternal stress and subsequent offspring ADHD risk. To my knowledge, neither of these postnatal parental stress measures have been included in previous studies.

The assessment of prenatal stress took place frequently (every two weeks) further minimizing recall-bias and ensuring that stress data was available for the whole pregnancy from week 12 onwards. However, some of the specificity was lost in the use of mean variables for each trimester and the pregnancy overall. Yet, the mean variables were comprised of up to 14 measurements, which far exceeds the number of data collection points used in previous studies (max. 6; Rodriguez & Bohlin, 2005) and adequately responds to earlier criticism of insufficient stress measurements (Lobel, 1994). Also, the reliability of the stress assessments improved with the use of several measurement points. The nature of the self-report stress evaluations may also be considered a strength, since subjective assessment of perceived stress has been found to be more strongly associated with offspring outcomes than objectively measured stress (Lipkind et al., 2010). Furthermore, the instruments chosen for both parental stress and child ADHD symptom appraisals have been commonly used and have shown good psychometric properties with high reliability and validity (Monroe, 2008; Nast et al., 2013; Rowe & Rowe, 1997). Also, the evaluation of child symptoms has been found to be more reliable when conducted by parents, as in the current study, as opposed to when performed by (kindergarten) teachers (Rowe & Rowe, 1997). However, the ability of mothers to assess child symptoms unbiased by their own stress levels may also be questionable (Monk et al., 2012). Therefore, among other reasons, postnatal maternal stress measured concurrently with child symptom assessment was included as a covariate in the present study.

A few limitations must also be noted. Despite the major strengths of using a prospective design, a common shortcoming also concerning the current study is attrition. The sample size was substantially reduced as a result of missing data, and especially so for the analyses including paternal stress measures. Nevertheless, the sample size remained much larger than the total sizes of most previous studies on the topic (Grizenko et al., 2008; Grizenko et al., 2012; Motlagh et al., 2010; Rice et al., 2010; Rodriguez & Bohlin, 2005). The women excluded from the present study differed from the ones included on age, education, pre-

pregnancy BMI, smoking, family structure, parity, child sex and partly on the levels of prenatal stress. However, the differences were small and concerned primarily covariates – women excluded from the study had significantly higher levels of stress only during the 2nd trimester and during pregnancy overall. No significant differences regarding child ADHD scores were found between the groups. Thus, although the women excluded from the study experienced, on average, more stress than the ones included, their children did not differ in their amount of ADHD symptoms, suggesting that the generalizability of the results remains good.

Another limitation is the imbalance in prenatal stress measurements over the course of pregnancy. The first assessment took place at weeks 12 + 0 to 13 + 6 constituting all data available for the first trimester. The second and third trimesters consisted of 7 and 6 measurements, respectively. The substantial difference in the amount – and thereby reliability – of data available for the first versus the latter trimesters may partly account for the weaker, and partly less significant, effects observed of early-pregnancy stress on child ADHD symptoms. However, as most research concerning the associations between prenatal stress and offspring psychological outcomes points to mid- to late-pregnancy stress to have the most prominent effects (Class et al., 2014; Laplante et al., 2008; Li et al., 2010; O'Connor et al., 2003; O'Donnell et al., 2014), the paucity of data of early-pregnancy stress in the current study may not have been as detrimental to the reliability of the analyses as limited late-pregnancy data would have been.

4.8 Conclusions

The current study is among the first and the most representative to offer strengthening evidence that maternal stress during pregnancy may alter the neurobehavioral development of the offspring from a large, community-based sample with reliable, prospective and frequent assessments of prenatal stress. The results indicate that exposure to prenatal maternal stress, in the form of general self-perceived stress, independently increases the risk of ADHD symptoms in toddlers and preschool-aged children, after controlling for several sociodemographic, prenatal, obstetric and postnatal factors. Maternal stress may be detrimental at any point during pregnancy, although the current findings suggest mid- to late-pregnancy stress to cast the most prominent effects on the offspring. Moreover, the present study provides valuable new information showing that the effects of prenatal maternal stress

on child ADHD symptoms may be partly mediated by postnatal maternal stress, highlighting the importance of accounting for a multitude of environmental factors concurrently.

The findings support the DOHaD-hypothesis (D. J. Barker, 1998) and underscore the significance of prenatal environmental factors in child development. Given that both maternal stress during pregnancy (Talge et al., 2007; Woods et al., 2010) and ADHD symptoms in children (Hinshaw, 2002; Willcutt, 2012) are common and associated with a wide array of other adversities, focusing preventive and therapeutic efforts on minimizing their adverse effects is of major importance for public health.

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Appendix 1. Correlations and mean differences between the main study variables and covariates.

	PSS overall		**PSS 1st trimester**		**PSS 2nd trimester**		**PSS 3rd trimester**		**Conners' ADHD**	
	r / MD	*p*	*r / MD*	*p*	*r / MD*	*p*	*r / MD*	*p*	*r / MD*	*p*
PSS 1-5 years	**.46**	**< .001**	**.36**	**< .001**	**.43**	**< .001**	**.43**	**< .001**	**.21**	**< .001**
PSS 6 months (father)	**.12**	**< .001**	**.09**	**.002**	**.12**	**< .001**	**.11**	**< .001**	**.06**	**.02**
Child variables										
Age	-.00	.90	-.02	.34	-.02	.32	.01	.56	**-.05**	**.03**
Sex	-0.02	.87	-0.09	.51	0.01	.92	-0.03	.77	**0.90**	**< .001**
Birthweight	.04	.06	.02	.31	.04	.07	**.07**	**.001**	**-.07**	**.001**
Length of gestation	**-.05**	**.03**	-.03	.12	-.02	.35	**-.07**	**.001**	-.02	.40
Maternal variables										
Age	-.04	.05	**-.05**	**.02**	**-.05**	**.03**	-.01	.78	**-.13**	**< .001**
Education (tertiary vs. lower)	**0.50**	**< .001**	**0.65**	**< .001**	**0.45**	**< .001**	**0.39**	**.001**	0.39	.05
Smoking (none vs. quit in 1st trim.)	**-1.01**	**.001**	**-1.53**	**< .001**	**-0.92**	**.003**	-0.61	.08	**-1.16**	**.04**
Smoking (none vs. smoked throughout)	**-0.77**	**.02**	-0.81	.06	**-0.74**	**.02**	**-0.88**	**.01**	**-1.95**	**.001**
Smoking (quit in 1st trim. vs. smoked throughout)	0.24	.62	0.72	.26	0.18	.72	-0.26	.63	-0.80	.39
Alcohol use (no vs. yes)	-0.17	.29	-0.22	.33	-0.21	.18	-0.06	.74	0.01	.96
BMI	**.07**	**.002**	.04	.07	**.08**	**< .001**	**.08**	**< .001**	-.01	.56
Parity (primiparous vs. multiparous)	**0.28**	**.009**	**0.32**	**.03**	0.17	.12	**0.38**	**.001**	**-1.04**	**< .001**
History of mental disorders (no vs. yes)	**-1.86**	**< .001**	**-2.08**	**< .001**	**-1.78**	**< .001**	**-1.68**	**< .001**	**-0.69**	**.02**
Hypertensive disorders (no vs. yes)	-0.26	.11	-0.20	.37	-0.04	.80	**-0.53**	**.008**	0.03	.92
Family structure (living with vs. without partner)	**1.52**	**.02**	**2.15**	**.01**	**1.43**	**.04**	0.87	.07	-0.11	.89

r = Pearson's correlation coefficient; *MD* = mean difference